DB Name	Query	Hit Count	Set Name
DWPI	l9 and (cancer or tumor$1 or tumour$1 or $carcinoma or $sarcoma or neoplasia or leukemia or $lymphoma or hodgkin or $myeloma)	43	L10
DWPI	leptin or (ob adj protein) or (obese adj protein)	169	L9
JPAB,EPAB	l7 and (cancer or tumor$1 or tumour$1 or $carcinoma or $sarcoma or neoplasia or leukemia or $lymphoma or hodgkin or $myeloma)	0	L8
JPAB,EPAB	l6 and @pd<19980426	45	L7
JPAB,EPAB	leptin or (ob adj protein) or (obese adj protein)	79	L6
USPT	l4 and @ad<19980426	13	L5
USPT	l1 with (cancer or tumor$1 or tumour$1 or $carcinoma or $sarcoma or neoplasia or leukemia or $lymphoma or hodgkin or $myeloma)	22	L4
USPT	l2 and @ad<19980426	28	L3
USPT	l1 same (cancer or tumor$1 or tumour$1 or $carcinoma or $sarcoma or neoplasia or leukemia or $lymphoma or hodgkin or $myeloma)	45	L2
USPT	leptin or (ob adj protein) or (obese adj protein)	207	L1

FILE 'MEDLINE' ENTERED AT 21:28:18 ON 03 OCT 2001

FILE 'BIOSIS' ENTERED AT 21:28:18 ON 03 OCT 2001
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FILE 'CANCERLIT' ENTERED AT 21:28:18 ON 03 OCT 2001

FILE 'LIFESCI' ENTERED AT 21:28:18 ON 03 OCT 2001
COPYRIGHT (C) 2001 Cambridge Scientific Abstracts (CSA)

=> s leptin or ((OB(w)protein) or (obese(w)protein))
   3 FILES SEARCHED...
L1   10815 LEPTIN OR ((OB(W) PROTEIN) OR (OBESE(W) PROTEIN))

=> s l1 and (cancer# or tumor# or tumour# or adenocarcinoma or carcinoma or sarcoma or myeloma or leukemia or lymphoma)
   3 FILES SEARCHED...
L2   1007 L1 AND (CANCER# OR TUMOR# OR TUMOUR# OR ADENOCARCINOMA OR CARCIN
             OMA OR SARCOMA OR MYELOMA OR LEUKEMIA OR LYMPHOMA)

=> s l3 and py<1999
L3 NOT FOUND
The L-number entered could not be found. To see the definition
of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s l2 and py<1999
   2 FILES SEARCHED...
L3   294 L2 AND PY<1999

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4   159 DUP REM L3 (135 DUPLICATES REMOVED)

WEST

Generate Collection

L10: Entry 35 of 43 File: DWPI Mar 6, 1998

DERWENT-ACC-NO: 1998-159462
DERWENT-WEEK: 199830

TITLE: New leptin and leptin-binding protein complex - useful for, e.g. diagnosis and treatment of leptin-related disorders such as obesity, anorexia, cancer or AIDS

INVENTOR: FRIEDMAN, J M; LALLONE, R

PRIORITY-DATA: 1996US-0699029 (August 16, 1996), 1996US-0023685 (August 16, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 9740758 A	March 6, 1998	N/A	000	C07K014/775
WO 9806752 A1	February 19, 1998	E	133	C07K014/775

INT-CL (IPC): A61K 38/22; C07K 14/575; C07K 14/775; C07K 16/18; C07K 16/26; G01N 33/68

ABSTRACTED-PUB-NO: WO 9806752A
BASIC-ABSTRACT:

A composition comprising a purified leptin and leptin binding protein (LBP), is new. LBP has the following characteristics: (a) it co-purifies with leptin when leptin is purified on a leptin affinity column; (b) it has a binding affinity for leptin, and (c) it has an apparent molecular weight of 80 kDa as determined by SDS-PAGE under non-reducing conditions and an apparent molecular weight of 40 kDa as determined by SDS-PAGE under reducing conditions. Also claimed are: (1) an antibody specific for an epitope created by the association of leptin and LBP; (2) a method of detecting leptin bound to a LBP in a sample, comprising: (a) contacting a sample with a binding partner specific for a leptin-LBP complex, under conditions that allow the binding partner to associate with leptin-LBP complex in the sample, and (b) detecting binding of the binding partner to the leptin-LBP complex: (3) a method for diagnosing an abnormality in the endogenous leptin pathway in a mammal, comprising: (a) determining the amount of a form of apolipoprotein J (AP-J) in the sample, and (b) comparing the amount of the form of AP-J determined in the biological sample to a range of amounts of the forms of AP-J determined in mammals having a normal endogenous leptin pathway; (4) a method of monitoring the treatment of an abnormality in the endogenous leptin pathway in a subject by

administering at least 1 dose of a composition comprising leptin and AP-J, comprising serially monitoring a value determined for a property of a biological sample acquired from the sample, where the property is selected from: (i) the quantity of leptin bound to AP-J; (ii) the quantity of leptin not bound to AP-J; (iii) a quantitative relationship between (i) and (ii), and (iv) a quantitative relationship between the quantity of total leptin and (i) or (ii), and (5) a kit for performing a method as in (2), comprising: (a) a container holding the first binding partner, and (b) a container holding the second binding partner.

USE - The products and methods can be used for diagnosing, monitoring and treating (claimed) abnormalities in the endogenous leptin pathway which regulate body weight and adiposity. They can provide for an increase in leptin activity and a decrease in body mass and in levels of fat. They can also be used for treating conditions associated with weight loss, such as anorexia, certain cancers and AIDS and diseases associated with obesity such as hypertension, heart disease, and Type II diabetes. In addition, there are potential agricultural uses for LBP in modulating the body weight of domestic animals.

BIOMEDICINE: Cancer Therapy on Target
Paula A. Kiberstis
Science 2001 April 20; 292: 399-401.

A major limitation of conventional cancer drugs is that they kill rapidly growing normal cells as well as cancer cells. Since the discovery that cancer cells contain specific molecular genetic alterations, researchers have labored to develop new therapies that target these alterations selectively, with the hope that such therapies would kill cancer cells primarily. In the case of chronic myeloid leukemia (CML), there is a chromosomal translocation (yielding the Philadelphia chromosome) that fuses two unrelated genes, BCR and ABL. This translocation creates a BCR-ABL fusion protein with a constitutive tyrosine kinase activity that has been shown to be causally involved in the disease. A small-molecule inhibitor of BCR-ABL, called STI571 (for the crystal structure of the ABL-STI571 complex, see Schindler et al., Reports, 15 Sept 2000, p. 1938) was designed in the early 1990s; it was brought to phase I clinical trials as an anticancer agent on the basis of promising results in cell culture studies and animal models. Druker et al. report the exciting and highly anticipated results of these clinical trials. When administered orally at a dose of 300 milligrams per day or higher, STI571 produced complete hematologic responses in 53 of 54 patients with early-stage CML (chronic phase) without serious side effects. In a second study, Druker et al. observed hematologic responses in 55 to 70% of patients with a more advanced stage of CML (blast crisis) or with acute lymphoblastic leukemia (ALL), although the responses were less durable than those seen in patients with chronic phase CML. Furthermore, cell culture studies had shown that STI571 inhibits the c-Kit tyrosine kinase, leading Joensuu et al. to test the efficacy of the drug in one patient with a gastrointestinal stromal tumor, a tumor type known to express the c-Kit kinase and for which there is no effective therapy. This patient also exhibited a strong response to the drug, showing a 52% decrease in tumor volume within 1 month. These findings offer great hope for the future success of targeted therapies for cancer.

L30 ANSWER 16 OF 29 CANCERLIT on STN
ACCESSION NUMBER: 96625855 CANCERLIT
DOCUMENT NUMBER: 96625855
TITLE: Constitutive phosphorylation of Shc is blocked by the C-erbB2 kinase inhibitor AG-879 in breast cancer cells (Meeting abstract).
AUTHOR: Stevenson L E; Frackelton A R Jr
CORPORATE SOURCE: Dept. Med. and Pathobiology, Roger Williams Hosp., Providence, RI 02908.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, **(1996)** 37 A375.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19970509
Last Updated on STN: 19970509

AB The consequences of upregulated receptor tyrosine kinases leads to Ras activation and cell growth. In some **breast cancers** both the epidermal growth factor receptor and C-erbB2 receptor tyrosine kinases are overexpressed and can be either stimulated by autocrine factors or are constitutively activated. With this in mind, **breast cancer** cell lines with these phenotypes may have constitutively activated downstream targets. One such example is constitutively activated downstream targets. One such example is constitutively phosphorylated Shc (50,56,60 kD), an adapter protein that interacts with phosphorylated tyrosines through its SH2 domain. Upon receptor binding, Shc is itself phosphorylated and acts as a docking site for **Grb2**:mSos. Either by Shc:**Grb2**:mSos or by **Grb2**:mSos alone, the extracellular signal is transmitted to activate Ras GTP/GDP exchange. We show that Shc is constitutively phosphorylated in several **breast cancer** cell lines that overexpress C-erbB2 (SK-BR-3, BT-474, MDA-MB-361, and MDA-MB-453). When these cells are treated with tyrphostin AG-879, a C-erb B2-specific tyrosine kinase inhibitor, constitutively phosphorylated Shc is also inhibited. In contrast, tyrphostin B56, and EGF-receptor-specific inhibitor, did not reduce Shc phosphorylation. These results suggest that it may be important to target not only growth factor receptors but downstream signaling proteins as well.

DUPLICATE 16

L30 ANSWER 28 OF 29 MEDLINE on STN

ACCESSION NUMBER: 94336228 MEDLINE
DOCUMENT NUMBER: 94336228 PubMed ID: 8058337
TITLE: Overexpression of the **Grb2** gene in human **breast cancer** cell lines.

AUTHOR: Daly R J; Binder M D; Sutherland R L
CORPORATE SOURCE: Cancer Biology Division, Garvan Institute of Medical Research, St. Vincent's Hospital, Sydney, N.S.W., Australia.

SOURCE: ONCOGENE, **(1994 Sep)** 9 (9) 2723-7.
Journal code: 8711562. ISSN: 0950-9232.

PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199409
ENTRY DATE: Entered STN: 19940920
Last Updated on STN: 20000303
Entered Medline: 19940915

AB A receptor blotting technique was used to detect SH2 domain containing epidermal growth factor receptor (EGFR) substrates that exhibited differential expression either between normal breast epithelial cells and breast cancer cells or between different human breast cancer cell lines. This identified a 25 kD protein, subsequently identified as **Grb2**, which was markedly overexpressed in three **breast cancer** cell lines (MCF-7, MDA-MB-361 and -453) relative to both normal breast epithelial cells and the majority of **breast cancer** cell lines. Northern blot analysis revealed that 7/19 **breast cancer** cell lines exhibited more than twofold overexpression of **Grb2** mRNA, with overexpression correlating with high expression of erbB receptors. In MCF-7, MDA-MB-361 and -453 cells the overexpression of Grb2 mRNA and protein was accompanied by a small amplification of the Grb2 gene locus. Overexpression of Grb2 correlated with increased complex formation between Grb2 and the hSos-1 Ras GDP-GTP exchange protein. This upregulation of the Ras signalling pathway might modulate the growth factor sensitivity of human breast cancer cells and therefore play a role in tumour progression.

L18 ANSWER 9 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 6

ACCESSION NUMBER: 1996:158164 BIOSIS
DOCUMENT NUMBER: PREV199698730299
TITLE: Overexpression of human insulin receptor substrate 1 induces cellular transformation with activation of mitogen-activated protein kinases.

AUTHOR(S): Ito, Toshifumi; Sasaki, Yutaka; Wands, Jack R. (1)
CORPORATE SOURCE: (1) Mol. Hepatol. Lab., MGH Cancer Cent., Build. 149, 13th St., 7th Floor, Charlestown, MA 02129 USA

SOURCE: Molecular and Cellular Biology, (1996) Vol. 16, No. 3, pp. 943-951.
ISSN: 0270-7306.

DOCUMENT TYPE: Article
LANGUAGE: English

AB The **insulin receptor substrate 1** protein (**IRS-1**) is a specific substrate for insulin receptor tyrosine kinase. Expression and tyrosyl phosphorylation of **IRS-1** play an important role during normal hepatocyte growth, and the gene is overexpressed in hepatocellular **carcinoma** tissue. We determined if **IRS-1** overexpression directly contributes to cellular transformation. The human **IRS-1** gene was subcloned into a mammalian expression vector driven by the cytomegalovirus early promoter. NIH 3T3 cells transiently transfected with this vector subsequently developed transformed foci. Several stably transfected cell lines were established, and they grew efficiently under low-serum conditions and formed colonies when plated in soft agar. Cell lines overexpressing **IRS-1** displayed increased tyrosyl phosphorylation of **IRS-1** and association with **Grb2** but not with the p85 subunit of phosphatidylinositol 3'-kinase. Since **Grb2** is a component of the son-of-sevenless-Ras pathway and upstream in the mitogen-activated protein kinase (MA-PK) cascade, enzymatic activities of the major components of this cascade, such as MAPK kinase and MAPK were evaluated and found to be substantially increased in three independent cell lines with **IRS-1** protein overexpression. Such cells, when injected into nude mice, were highly **tumorigenic**, and there may be a correlation between the degree of MAPK activation and **tumor** growth rate. This report describes the generation of a transformed phenotype by overexpression of a molecule without a catalytic domain far upstream in the signal transduction cascade and suggests that prolonged activation of MAPKs by this mechanism may be one of the molecular events related to hepatocellular transformation.

L30 ANSWER 25 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 14

ACCESSION NUMBER: 1996:35650 BIOSIS
DOCUMENT NUMBER: PREV199698607785
TITLE: Heregulin (HRG)-induced mitogenic signaling and cytotoxic activity of a HRG/PE40 ligand toxin in human breast cancer cells.
AUTHOR(S): Fiddes, Rodney J.; Janes, Peter W.; Sanderson, Georgina M.; Sivertsen, Susan P.; Sutherland, Robert L.; Daly, Roger J. (1)
CORPORATE SOURCE: (1) Co-Operative Research Centre Biopharmaceutical Research, Garvan Inst. Med. Research, St. Vincent's Hosp., Sydney, NSW 2010 Australia
SOURCE: Cell Growth & Differentiation, (1995) Vol. 6, No. 12, pp. 1567-1577.
ISSN: 1044-9523.
DOCUMENT TYPE: Article
LANGUAGE: English

AB The heregulins (HRGs) are a family of growth factors that bind directly to erbB3 and erbB4 and induce tyrosine phosphorylation of erbB2 via receptor heterodimerization. Since erbB2, erbB3, and erbB4 (erbB2-4) are often overexpressed in human **breast cancer** cells, we produced recombinant HRGs and a HRG-based ligand toxin to investigate the signaling events triggered by HRGs and the ability of these ligands to specifically target such cells. Recombinant HRG-beta-2 stimulated the tyrosine phosphorylation of erbB2-4 in ZR-75-1 human **breast cancer** cells. This was accompanied by the tyrosine phosphorylation of Shc and the formation of complexes between Shc and the adapter protein **Grb2**. Complexes were also detected between Shc and erbB2-4. However, **Grb2** was detected in erbB2 and erbB4 but not erbB3 immunoprecipitates. Thus, these receptors exhibit mechanistic differences in their coupling to Ras signaling, and HRG-beta-2 administration triggers multiple inputs into the Ras signaling pathway, involving receptor-**Grb2**, receptor-Shc, and Shc-**Grb2** complexes. HRG-beta-2 addition also stimulated the association of erbB3 with phosphatidylinositol-3-kinase. In accordance with the activation of key mitogenic signaling pathways, HRG-beta-2 stimulated the proliferation of MCF-7 and T-47D human **breast cancer** cells. Moreover, when tested for the ability to stimulate cell cycle re-entry of T-47D cells arrested under serum-free conditions, HRG-beta-2 was more effective than insulin, previously the most potent mitogen identified using this system. Finally, a HRG-beta-2/PE40 ligand toxin was constructed and found to exhibit cytotoxic activity against human **breast cancer** cells overexpressing erbB3 alone or in combination with erbB4 and/or erbB2.

TITLE: Activation of the Ras signalling pathway in human breast cancer cells overexpressing erbB-2.

AUTHOR: Janes P W; Daly R J; deFazio A; Sutherland R L
CORPORATE SOURCE: Cancer Biology Division, Garvan Institute of Medical Research, St Vincent's Hospital, Sydney, NSW, Australia.

SOURCE: ONCOGENE, **(1994 Dec)** 9 (12) 3601-8.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 20000303
Entered Medline: 19941220

AB The c-erbB-2 proto-oncogene encodes a receptor tyrosine kinase (RTK) closely related to the epidermal growth factor receptor (EGFR). Overexpression of erbB-2 occurs in approximately 20% of human breast tumours, where increased expression correlates with poor patient prognosis. The EGFR is coupled to the Ras signalling pathway by interaction with the adaptor protein Grb2, and Sos, a Ras GDP-GTP exchange factor. In this study, activation of the erbB-2 receptor and its association with **Grb2** and Sos was investigated in **breast cancer** cell lines which overexpress erbB-2. The receptor was found to be tyrosine phosphorylated in all cell lines in which it is overexpressed. Western blotting of Grb2 and Sos immuneprecipitates from such cells revealed co-precipitation of erbB-2, demonstrating association of the Grb2/Sos complex with erbB-2 in vivo. Furthermore, a fusion protein containing only the SH2 domain of Grb2 bound to erbB-2 immobilized on nitrocellulose, indicating that association with Grb2 is direct and mediated by the SH2 domain of Grb2. The degree of association between the erbB-2 receptor and Grb2 in vivo was related to erbB-2 overexpression, and MAP kinase, which functions downstream from Ras, displayed markedly increased activity in cell lines overexpressing erbB-2. These results demonstrate that erbB-2 is coupled to Ras signalling via the **Grb2**. /Sos complex, and that overexpression of this receptor in **breast cancer** cells leads to amplification of the Ras signalling pathway.

DUPLICATE 5

L30 ANSWER 8 OF 29 MEDLINE on STN

ACCESSION NUMBER: 97162175 MEDLINE
DOCUMENT NUMBER: 97162175 PubMed ID: 9009162
TITLE: Multiple Grb2-protein complexes in human cancer cells.
AUTHOR: Sastry L; Cao T; King C R
CORPORATE SOURCE: Department of Biochemistry, Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC 20007. USA.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, **(1997 Jan 17)** 70 (2) 208-13.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 20000303
Entered Medline: 19970220

AB Grb2 is an SH2/SH3 domain-containing adaptor protein that links receptor tyrosine kinases to the ras signaling pathway. The Grb2-SH2 domain binds phosphotyrosine sequences on activated tyrosine kinases, and one target of the SH3 domains is the ras-nucleotide-exchange factor Sos1. We have examined Grb2-protein interactions in human cancer cells that over-express the receptor tyrosine kinase erbB2. Our results show that the 2 Grb2-SH3 domains complex with Sos1, dynamin and at least 4 other proteins (p228, p140, p55, p28) in these cells. The 2 Grb2-SH3 domains bind these proteins differently, with the N-terminal SH3 domain interacting preferentially with p228, Sos1, p140 and dynamin. The C-terminal SH3 domain has higher affinity toward p28. The **Grb2**-SH3 domain interactions appear to be similar in erbB2 over-expressing **breast**, ovarian and lung **cancer** cells. Also, the major tyrosine-phosphorylated proteins that associate with Grb2 in erbB2 over-expressing cancer cells appear to be erbB2 and Shc. The multiple Grb2-SH3 domain interactions in these cells may mediate novel cellular functions.

4/2/98

DUPLICATE 1

L4 ANSWER 1 OF 159 MEDLINE
ACCESSION NUMBER: 1999045319 MEDLINE
DOCUMENT NUMBER: 99045319 PubMed ID: 9829854
TITLE: Serum **leptin** levels during **cancer** chemotherapy.
AUTHOR: Usuki K; Okazaki R; Iki S; Muramatsu M; Yamaguchi Y; Totsuka Y; Urabe A
SOURCE: ANNALS OF HEMATOLOGY, **(1998 Oct)** 77 (4) 191-2. Journal code: A2P; 9107334. ISSN: 0939-5555.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981210

DUPLICATE 2

L4 ANSWER 2 OF 159 MEDLINE
ACCESSION NUMBER: 1999049616 MEDLINE
DOCUMENT NUMBER: 99049616 PubMed ID: 9833870
TITLE: Bound **leptin** is regulated by **tumour** necrosis factor-alpha in HIV-infected patients: a potential mediator of wasting?.
AUTHOR: Ockenga J; Widjaja A; Holtmannspotter M; Schmidt R E; Brabant G
SOURCE: AIDS, **(1998 Nov 12)** 12 (16) 2233-5. Journal code: AID; 8710219. ISSN: 0269-9370.
PUB. COUNTRY: United States
Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990216
Last Updated on STN: 20000303
Entered Medline: 19990129

L4 ANSWER 3 OF 159 CANCERLIT
ACCESSION NUMBER: 1999045319 CANCERLIT
DOCUMENT NUMBER: 99045319
TITLE: Serum **leptin** levels during **cancer** chemotherapy [letter].
AUTHOR: Usuki K; Okazaki R; Iki S; Muramatsu M; Yamaguchi Y; Totsuka Y; Urabe A
SOURCE: ANNALS OF HEMATOLOGY, **(1998)**. Vol. 77, No. 4, pp. 191-2. Journal code: A2P. ISSN: 0939-5555.
DOCUMENT TYPE: Letter
FILE SEGMENT: MEDL; L; Priority Journals; Cancer Journals
LANGUAGE: English
OTHER SOURCE: MEDLINE 99045319
ENTRY MONTH: 199901

L4 ANSWER 4 OF 159 CANCERLIT
ACCESSION NUMBER: 1999049616 CANCERLIT
DOCUMENT NUMBER: 99049616

TITLE: Bound **leptin** is regulated by **tumour** necrosis factor-alpha in HIV-infected patients: a potential mediator of wasting? [letter].
AUTHOR: Ockenga J; Widjaja A; Holtmannspotter M; Schmidt R E; Brabant G
SOURCE: AIDS, **(1998)**. Vol. 12, No. 16, pp. 2233-5. Journal code: AID. ISSN: 0269-9370.
DOCUMENT TYPE: Letter
FILE SEGMENT: MEDL; L; Priority Journals
LANGUAGE: English
OTHER SOURCE: MEDLINE 99049616
ENTRY MONTH: 199903

L4 ANSWER 5 OF 159 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999076819 MEDLINE
DOCUMENT NUMBER: 99076819 PubMed ID: 9859722
TITLE: [The auto- and endocrine function of the adipose tissue. Significance for metabolic complications in obesity]. Fedtvaevets auto- og endokrine funktion. Betydning for de metaboliske komplikationer ved adipositas.
AUTHOR: Richelsen B; Kristensen K; Jensen J D
CORPORATE SOURCE: Arhus Universitetshospital, Arhus Amtssygehus, medicinsk-endokrinologisk afdeling C.. br@aas.auh.dk
SOURCE: UGESKRIFT FOR LAEGER, **(1998 Dec 7)** 160 (50) 7246-50. Ref: 28
Journal code: WM8; 0141730. ISSN: 0041-5782.
PUB. COUNTRY: Denmark
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Danish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990202
Last Updated on STN: 19990202
Entered Medline: 19990119

AB The present review discusses recent research showing adipose tissue to be highly metabolically active, producing and releasing many different bioactive compounds besides free fatty acids (FFA) such as **tumor** necrosis factor alpha (TNF alpha), **leptin**, acetylation stimulating protein (ASP), plasminogen activator inhibitor-1 (PAI-1), cholesterol ester transfer protein (CETP), prostaglandins and oestrogens. Most of these compounds have autocrine effects on the adipose cells and they are presumably involved in the physiological regulation of blood flow, growth and metabolism of the adipose tissue. When the adipose tissue becomes enlarged, as seen in association with obesity, it has now been shown that several of the compounds produced in the adipose tissue (TNF, PAI-1, CETP etc.) may be directly involved in the pathogenesis of some of the complications commonly seen in association with obesity such as insulin resistance, hypertension, enhanced thrombogenesis, and premature atherosclerosis.

L4 ANSWER 6 OF 159 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1999016829 MEDLINE
DOCUMENT NUMBER: 99016829 PubMed ID: 9800447
TITLE: [Double role of appetite stimulants. **Leptin** may

be of significance also for vascular growth in **tumors**].
Dubbla roller for aptitreglerare. **Leptin** kan aven ha betydelse for karltillvaxt i tumorer.

AUTHOR: Orn P
SOURCE: LAKARTIDNINGEN, **(1998 Sep 30)** 95 (40) 4323.
Journal code: L0N; 0027707. ISSN: 0023-7205.
PUB. COUNTRY: Sweden
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Swedish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981109

L4 ANSWER 7 OF 159 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999029629 MEDLINE
DOCUMENT NUMBER: 99029629 PubMed ID: 9814492
TITLE: Intact **leptin** receptor is selectively expressed in human fetal pituitary and pituitary adenomas and signals
human fetal pituitary growth hormone secretion.
AUTHOR: Shimon I; Yan X; Magoffin D A; Friedman T C; Melmed S
CORPORATE SOURCE: Department of Medicine, Cedars-Sinai Research Institute-University of California School of Medicine, Los Angeles 90048, USA.
CONTRACT NUMBER: DA-00276 (NIDA)
DK-50238 (NIDDK)
HD-33907 (NICHD)
SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, **(1998 Nov)** 83 (11) 4059-64.
Journal code: HRB; 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981125

AB **Leptin**, a circulating hormone secreted by adipocytes, communicates peripheral nutritional status to hypothalamic centers affecting satiety, energy expenditure, and body weight. The intact **leptin** receptor (OB-R), a single membrane-spanning peptide containing an approximately 300-amino acid intracellular domain, is highly expressed in the hypothalamus, whereas shorter OB-R isoforms with truncated cytoplasmic regions resulting from alternative splicing have also been identified. We studied expression of OB-R isoforms in human fetal pituitaries, adult anterior pituitaries, and human pituitary adenomas. Using RT-PCR, messenger ribonucleic acid expression of the OB-R intact isoform was detected in fetal anterior pituitary tissues, but not in adult anterior pituitary glands, whereas both fetal and adult tissues expressed the short forms. Messenger ribonucleic acid of both intact and short OB-R isoforms were expressed in 4 of 5 GH-secreting, all 9 PRL-secreting, and 26 of 29 nonfunctioning pituitary adenomas. Recombinant

human **leptin** (3-6 nmol/L) specifically stimulated GH secretion from primary human fetal pituitary cultures by 40-90% ($P < 0.05$) without altering fetal ACTH, PRL, or gonadotropin secretion. Thus, the intact OB-R is selectively expressed in human fetal and adult pituitary **tumor** tissues, but not in normal adult pituitary. **Leptin** specifically stimulates GH release from normal fetal somatotrophs, substantiating the functionality of its intact receptor in the fetal pituitary. Thus, pituitary adenomas appear to revert to a fetal phenotype of **leptin** receptor expression.

L4 ANSWER 8 OF 159 LIFESCI COPYRIGHT 2001 CSA
ACCESSION NUMBER: 1999:29240 LIFESCI
TITLE: Insulin resistance and diabetes mellitus in transgenic mice expressing nuclear SREBP-1c in adipose tissue: model for congenital generalized lipodystrophy
AUTHOR: Shimomura, I.; Hammer, R.E.; Richardson, J.A.; Ikemoto, S.; Bashmakov, Y.; Goldstein, J.L.; Brown, M.S.
CORPORATE SOURCE: Department of Molecular Genetics, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas 75235 USA; E-mail: jgolds@mednet.swmed.edu
SOURCE: Genes & Development, (**19981015**) vol. 12, no. 20, pp. 3182-3194.
ISSN: 0890-9369.
DOCUMENT TYPE: Journal
FILE SEGMENT: G
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Overexpression of the nuclear form of sterol regulatory element-binding protein-1c (nSREBP-1c/ADD1) in cultured 3T3-L1 preadipocytes was shown previously to promote adipocyte differentiation. Here, we produced transgenic mice that overexpress nSREBP-1c in adipose tissue under the control of the adipocyte-specific aP2 enhancer/promoter. A syndrome with the following features was observed: (1) Disordered differentiation of adipose tissue. White fat failed to differentiate fully, and the size of white fat depots was markedly decreased. Brown fat was hypertrophic and contained fat-laden cells resembling immature white fat. Levels of mRNA encoding adipocyte differentiation markers (C/EBP alpha , PPAR gamma , adipsin, **leptin**, UCP1) were reduced, but levels of Pref-1 and TNF alpha were increased. (2) Marked insulin resistance with 60-fold elevation in plasma insulin. (3) Diabetes mellitus with elevated blood glucose (>300 mg/dl) that failed to decline when insulin was injected. (4) Fatty liver from birth and elevated plasma triglyceride levels later in life. These mice exhibit many of the features of congenital generalized lipodystrophy (CGL), an autosomal recessive disorder in humans.

DUPLICATE 6

L4 ANSWER 9 OF 159 MEDLINE
ACCESSION NUMBER: 1999081506 MEDLINE
DOCUMENT NUMBER: 99081506 PubMed ID: 9865908
TITLE: Effect of weight loss and the inflammatory response on **leptin** concentrations in gastrointestinal **cancer** patients.
AUTHOR: Wallace A M; Sattar N; McMillan D C
CORPORATE SOURCE: University Department of Clinical Biochemistry, Royal Infirmary, Glasgow, United Kingdom..

awallace@clinmed.gla.ac.uk
SOURCE: CLINICAL CANCER RESEARCH, **(1998 Dec)** 4 (12) 2977-9.
Journal code: C2H; 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990402
Last Updated on STN: 20000303
Entered Medline: 19990322

AB Animal research suggests that **leptin** may have an important role in the regulation of energy balance. The role of **leptin** in the progressive involuntary weight loss associated with **cancer** in humans is of considerable interest. However, such studies are limited. In this study, we compared circulating **leptin** concentrations in gastrointestinal **cancer** patients and weight loss (n = 27) with those of healthy subjects (n = 27). The effect of the presence of an inflammatory response on **leptin** concentrations was also examined. There were significantly lower **leptin** concentrations in male (median, 2.4 microg/liter; range, <0.5-6.0 microg/liter) and female (median, 3.4 microg/liter; range, <0.5-9.8 microg/liter) **cancer** patients than there were in male (median, 6.5 microg/liter; range, 3.1-10.9 microg/liter) and female (median, 18.7 microg/liter; range, 8.0-31.5 mcirog/liter) healthy subjects (P < 0.001). However, the **leptin** concentrations in both patients and normal subjects were related to the predicted percentage of body fat (r = 0.731; P < 0.001). Circulating **leptin** concentrations in the **cancer** patients were not altered by the presence of an inflammatory response. These results suggest that **cancer** anorexia/cachexia is not due to a simple dysregulation of **leptin** production.

DUPLICATE 7

L4 ANSWER 10 OF 159 MEDLINE

ACCESSION NUMBER: 1998224505 MEDLINE
DOCUMENT NUMBER: 98224505 PubMed ID: 9564834
TITLE: In vivo and in vitro evidence for the involvement of **tumor** necrosis factor-alpha in the induction of **leptin** by lipopolysaccharide.
AUTHOR: Finck B N; Kelley K W; Dantzer R; Johnson R W
CORPORATE SOURCE: Department of Animal Sciences, University of Illinois, Urbana 61801, USA.
CONTRACT NUMBER: DK-49311 (NIDDK)
DK-51576 (NIDDK)
SOURCE: ENDOCRINOLOGY, **(1998 May)** 139 (5) 2278-83.
Journal code: EGZ; 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980520
Last Updated on STN: 20000303
Entered Medline: 19980508

AB To examine the role of **tumor** necrosis factor-alpha (TNF alpha) in mediating **leptin** secretion during an immunological challenge, we studied the effects of lipopolysaccharide (LPS) and TNF alpha on

leptin secretion in endotoxin-sensitive C3H/HeOuJ (OuJ) mice, endotoxin-insensitive C3H/HeJ (HeJ) mice, and primary adipocytes cultured from both. Intraperitoneal injection of LPS increased plasma concentrations of TNF alpha and **leptin** in OuJ mice, but not in HeJ mice, suggesting a causal relationship between the induction of TNF alpha and **leptin**. Consistent with this idea, i.p. injection of recombinant murine TNF alpha increased plasma **leptin** in both OuJ and HeJ mice. To determine whether TNF alpha induces **leptin** secretion by acting directly on fat cells, primary adipocytes from OuJ

and

HeJ mice were cultured in the presence of TNF alpha or LPS. Whereas LPS was without effect on **leptin** secretion by adipocytes, TNF alpha induced a marked increase in the cell supernatant **leptin** concentration. These data demonstrate that TNF alpha plays a role in regulating the increase in **leptin** caused by LPS. Moreover, they show that TNF alpha can act directly on adipocytes to stimulate **leptin** secretion. Our results are consistent with the emerging view that **leptin** is a key hormone coupling immune system activity to energy balance.

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L4 ANSWER 11 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:254987 BIOSIS
DOCUMENT NUMBER: PREV199800254987
TITLE: In vivo and in vitro evidence for the involvement of **tumor** necrosis factor-alpha in the induction of **leptin** by lipopolysaccharide.
AUTHOR(S): Finck, Brian N.; Kelley, Keith W.; Dantzer, Robert; Johnson, Rodney W. (1)
CORPORATE SOURCE: (1) 390 Anim. Sci. Lab., Univ. Illinois, 1207 West Gregory Drive, Urbana, IL 61801 USA
SOURCE: Endocrinology, (**May**, **1998**) Vol. 13, No. 5, pp. 2278-2283.
ISSN: 0013-7227.
DOCUMENT TYPE: Article
LANGUAGE: English
AB To examine the role of **tumor** necrosis factor-alpha (TNFalpha) in mediating **leptin** secretion during an immunological challenge, we studied the effects of lipopolysaccharide (LPS) and TNFalpha on **leptin** secretion in endotoxin-sensitive C3H/HeOuJ (OuJ) mice, endotoxin-insensitive C3H/HeJ (HeJ) mice, and primary adipocytes cultured from both. Intraperitoneal injection of LPS increased plasma concentrations of TNFalpha and **leptin** in OuJ mice, but not in HeJ mice, suggesting a causal relationship between the induction of TNFalpha and **leptin**. Consistent with this idea, ip injection of recombinant murine TNFalpha increased plasma **leptin** in both OuJ and HeJ mice. To determine whether TNFalpha induces **leptin** secretion by acting directly on fat cells, primary adipocytes from OuJ

and

HeJ mice were cultured in the presence of TNFalpha or LPS. Whereas LPS

was

without effect on **leptin** secretion by adipocytes, TNFalpha-induced a marked increase in the cell supernatant **leptin** concentration. These data demonstrate that TNFalpha plays a role in regulating the increase in **leptin** caused by LPS. Moreover, they show that TNFalpha can act directly on adipocytes to stimulate

leptin secretion. Our results are consistent with the emerging view that **leptin** is a key hormone coupling immune system activity to energy balance.

L4 ANSWER 12 OF 159 LIFESCI COPYRIGHT 2001 CSA
ACCESSION NUMBER: 1999:24095 LIFESCI
TITLE: Bound **leptin** is regulated by **tumour** necrosis factor- alpha in HIV-infected patients: a potential mediator of wasting?
AUTHOR: Ockenga, J.; Widjaja, A.; Holtmannspoetter, M.; Schmidt, R.E.; Brabant, G.
CORPORATE SOURCE: Department of Gastroenterology, Medical School Hannover, 30623 Hannover, Germany
SOURCE: AIDS, (**19981112**) vol. 12, no. 16, pp. 2233-2234. ISSN: 0269-9370.
DOCUMENT TYPE: Journal
FILE SEGMENT: V
LANGUAGE: English
AB Malnutrition is a common feature during the course of HIV infection and is often related to anorexia due to acute opportunistic infections. The immune response to infection includes an increase in cytokines, such as **tumour** necrosis factor (TNF)- alpha , interleukin (IL)-1 or IL-6, which have been proposed to be involved in the pathogenesis of wasting syndrome in AIDS and other infectious diseases. The aim of the present study was to delineate a potential relationship between TNF- alpha and **leptin** in HIV-infected patients with acute infection.

L4 ANSWER 13 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:23522 BIOSIS
DOCUMENT NUMBER: PREV199900023522
TITLE: Corporeal veno-occlusive dysfunction: A distal arterial pathology.
AUTHOR(S): Wespes, E. (1); Raviv, G.; Vanegas, J.-P.; Decaestecker, C.; Petein, M.; Danguy, A.; Schulman, C. C.; Kiss, R.
CORPORATE SOURCE: (1) Dep. Urol., Erasme Hosp., Univ. Libre de Bruxelles, Brussels Belgium
SOURCE: Journal of Urology, (**Dec.**, **1998**) Vol. 160, No. 6 PART 1, pp. 2054-2057. ISSN: 0022-5347.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Purpose: Alteration of intracavernous smooth muscle cells has been demonstrated in patients with pure venous leakage. This modification seems correlated with reduction of intracavernous oxygen tension. However, Doppler imaging of the cavernous arteries in these patients is normal. To understand the ischemic factor we studied the endothelium of the terminal arteries with computerized image analysis and immunohistochemical staining with 2 types of lectin in patients with venous leakage and those with normal erections. Lectins are glycoproteins that can be used as histological markers to monitor functional and pathological changes. Materials and Methods: Four patients 44 to 59 years old with normal erections who were operated on for penile **cancer** and 11 patients 27 to 62 years old with pure venous leakage (flow to maintain erection greater than 15 ml. per minute and cavernous flow velocity greater than

cm. per second) were included in the study. Immunohistochemical staining with 2 lectins, wheat germ agglutinin and Ulex europeaus agglutinin I, was performed and analyzed with computerized image analysis. The labeling index which relates to the percentage of staining indicates the distribution of the endothelial cells, and mean optical density which relates to the staining intensity indicates the function of these cells. Results: Mean labeling index values for the 2 lectins were similar in both groups ($p > 0.05$). Mean optical density values for the 2 lectins were significantly greater for the patients with normal erections ($p < 0.01$). Therefore, the distribution of the endothelial cells was the same while their function was different in patients with corporeal veno-occlusive dysfunction. Conclusions: Staining with wheat germ agglutinin and Ulex europeaus agglutinin I lectin types allowed us to detect alteration in the glyco-histochemistry of the endothelial cells of the small arteries, and venous leakage could be the first step in vasculogenic impotence.

L4 ANSWER 14 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1999:91330 BIOSIS
DOCUMENT NUMBER: PREV199900091330
TITLE: Brain **tumor** development in rats is associated with changes in CNS cytokine and neuropeptide systems.
AUTHOR(S): Ilyin, S. E.; Gayle, D.; Turrin, N. P.; Flynn, M. C.; Plata-Salaman, C. R.
CORPORATE SOURCE: Div. Mol. Biol., SLHS, Univ. Del., Newark, DE 19716 USA
SOURCE: Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 1858.
Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 2 Los Angeles, California, USA November 7-12, 1998 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 15 OF 159 MEDLINE DUPLICATE 8

ACCESSION NUMBER: 1998187967 MEDLINE
DOCUMENT NUMBER: 98187967 PubMed ID: 9529118
TITLE: Increased **leptin** expression in mice with bacterial peritonitis is partially regulated by **tumor** necrosis factor alpha.
AUTHOR: Moshyedi A K; Josephs M D; Abdalla E K; Mackay S L; Edwards C K 3rd; Copeland E M 3rd; Moldawer L L
CORPORATE SOURCE: Department of Surgery, University of Florida College of Medicine, Gainesville 32610, USA.
CONTRACT NUMBER: GM-40586 (NIGMS)
GM-53252 (NIGMS)
SOURCE: INFECTION AND IMMUNITY, **(1998 Apr)** 66 (4) 1800-2.
Journal code: GO7; 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980416
Last Updated on STN: 20000303

Entered Medline: 19980409

AB Plasma **leptin** and ob gene mRNA levels were increased in mice following bacterial peritonitis, and blocking an endogenous **tumor** necrosis factor alpha (TNF-alpha) response blunted the increase. However, plasma **leptin** concentrations did not correlate with the associated anorexia. We conclude that **leptin** expression is under partial regulatory control of TNF-alpha in peritonitis, but the anorexia is not dependent on increased **leptin** production.

DUPLICATE 9

L4 ANSWER 16 OF 159 MEDLINE

ACCESSION NUMBER: 1998424224 MEDLINE
DOCUMENT NUMBER: 98424224 PubMed ID: 9753302
TITLE: Increased OB gene expression leads to elevated plasma **leptin** concentrations in patients with chronic primary hyperinsulinemia.
AUTHOR: D'Adamo M; Buongiorno A; Maroccia E; Leonetti F; Barbetti F; Giaccari A; Zorretta D; Tamburrano G; Sbraccia P
CORPORATE SOURCE: Department of Clinical and Experimental Medicine, University of Catanzaro, Italy.
SOURCE: DIABETES, **(1998 Oct)** 47 (10) 1625-9. Journal code: E8X; 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981021
Last Updated on STN: 20000303
Entered Medline: 19981009

AB **Leptin**, a hormone secreted by adipocytes, decreases food intake and increases energy expenditure. The role of insulin in the regulation of **leptin** secretion is poorly understood and is still a topic of debate. Insulin increases **leptin** mRNA synthesis in rodents, but in humans, the available data are discordant. To investigate the role of chronic hyperinsulinemia in the regulation of plasma **leptin** concentrations, we studied 13 patients with surgically confirmed insulinoma before and after **tumor** removal, along with 15 healthy control subjects matched for sex, age, and BMI. Immunoreactive plasma **leptin** levels were measured by radioimmunoassay; **leptin** mRNA levels were also determined by reverse transcription-competitive polymerase chain reaction in a subgroup of six patients with insulinoma and six control subjects. All determinations were made with subjects in the fasting state. Plasma **leptin** concentrations correlated positively with **leptin** mRNA levels ($r = 0.880$, $P < 0.001$). **Leptin** levels, both plasma protein and mRNA, were significantly higher in the insulinoma patients than in the control subjects (plasma protein: 17.5 +/- 3.6 vs. 2.9 +/- 0.4 ng/ml, respectively, $P < 0.001$; mRNA: 0.98 +/- 0.33 vs. 0.19 +/- 0.064 amol/microg RNA, respectively, $P < 0.05$), and they correlated positively with fasting plasma insulin levels in the patients with insulinoma (plasma protein: $r = 0.686$, $P < 0.01$; mRNA: 0.796, $P < 0.05$). Finally, removal of the insulin-secreting **tumor** was followed by the normalization of plasma **leptin** levels. In summary, in patients with insulinoma, 1) plasma **leptin** levels and **leptin** mRNA are elevated; 2) a direct relationship exists between **leptin**, both circulating protein and mRNA, and insulin concentrations; and 3) plasma **leptin** returns to normal levels after **tumor** removal. These data, therefore, support a

role for insulin in the chronic regulation of **leptin** gene expression.

L4 ANSWER 17 OF 159 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1998318532 MEDLINE
DOCUMENT NUMBER: 98318532 PubMed ID: 9608004
TITLE: **Leptin** produces anorexia and weight loss without inducing an acute phase response or protein wasting.
AUTHOR: Kaibara A; Moshyedi A; Auffenberg T; Abouhamze A; Copeland E M 3rd; Kalra S; Moldawer L L
CORPORATE SOURCE: Department of Surgery, University of Florida College of Medicine, Gainesville, Florida 32610, USA.
CONTRACT NUMBER: GM-40586 (NIGMS)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, **(1998 Jun)** 274 (6 Pt 2) R1518-25.
Journal code: 3U8; 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 20000303
Entered Medline: 19981105

AB The ob gene product **leptin** is known to produce anorexia and loss of body fat when chronically administered to both lean and genetically obese mice. The current study was undertaken to examine whether administration of recombinant **leptin** in quantities sufficient to produce decreases in food intake and body weight and alterations in body composition would elicit either an hepatic acute phase protein response or preferential loss of carcass lean tissue. Mice were administered increasing quantities of recombinant human **leptin** or human **tumor** necrosis factor-alpha as a positive control. Although **leptin** (at 10 mg/kg body wt) produced significant anorexia and weight loss (both $P < 0.05$), human **leptin** administration did not appear to induce an hepatic acute phase protein response in either lean or genetically obese mice, as determined by protein synthetic rates in the liver or changes in the plasma concentration of the murine acute phase protein reactants, amyloid A, amyloid P, or seromucoid (alpha1-acid glycoprotein). In addition, human **leptin** administration did not induce a loss of fat-free dry mass (protein) in lean or obese animals. The findings suggest that at doses adequate to alter food intake and body weight **leptin** is not a significant inducer of the hepatic acute phase response nor does **leptin** promote the preferential loss of somatic protein characteristic of a chronic inflammatory process.

L4 ANSWER 18 OF 159 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 1998392826 MEDLINE
DOCUMENT NUMBER: 98392826 PubMed ID: 9726225
TITLE: Depot-related gene expression in human subcutaneous and omental adipocytes.
AUTHOR: Montague C T; Prins J B; Sanders L; Zhang J; Sewter C P; Digby J; Byrne C D; O'Rahilly S
CORPORATE SOURCE: Department of Medicine, University of Cambridge, England, UK.. carl.montague@alderley.zeneca.com

SOURCE: DIABETES, **(1998 Sep)** 47 (9) 1384-91.
Journal code: E8X; 0372763. ISSN: 0012-1797.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980925
Last Updated on STN: 20000303
Entered Medline: 19980916

AB Human omental adipocytes display a range of biochemical properties that distinguish them from adipocytes of subcutaneous origin. However, information about site-related gene expression in human fat cells is limited. We have previously demonstrated that **leptin** mRNA is markedly overexpressed in abdominal subcutaneous (SC) compared with omental (Om) adipocytes. To further investigate depot-specific differences in adipocyte gene expression, we have measured, in paired samples of isolated human adipocytes obtained from SC and Om fat depots, the expression of mRNAs encoding a number of proteins involved in the control of adipocyte metabolism. In contrast to the marked site-related expression of **leptin**, genes encoding lipoprotein lipase (LPL), hormone-sensitive lipase (HSL), peroxisome proliferator-activated receptor-gamma (PPAR-gamma), **tumor** necrosis factor-alpha (TNF-alpha), and adipsin were not consistently differentially expressed. Of note, a highly significant inverse correlation between adipocyte PPAR-gamma expression and BMI ($r = -0.7$, $P = 0.0005$) was found. In parallel experiments, differential display was used in an attempt to identify novel and/or unexpected adipocyte genes that were expressed in a site-related manner. No transcript that was unique to one or another depot was found, but cellular inhibitor of apoptosis protein-2 (cIAP2) mRNA, which has not previously been reported in adipocytes, was expressed at higher levels in Om than SC adipocytes (Om > SC in all eight subjects; mean Om:SC ratio 1.9 +/- 0.2, $P < 0.01$). Because cIAP2 may be involved in the regulation of TNF-alpha signaling, this raises the possibility that depot-specific differences may exist in the regulation of adipocyte apoptosis. Thus, of the mRNAs examined to date, only **leptin** and cIAP2 show consistent site-related expression, suggesting that these molecules may have important roles in determining functional properties particular to individual adipose depots. Given the importance of PPAR-gamma in adipocyte development and insulin sensitivity, the inverse correlation between adipocyte PPAR-gamma mRNA levels and adiposity may represent a local regulatory mechanism restraining fat accumulation and/or may be related to the reduction of insulin sensitivity that occurs with increasing fat mass.

L4 ANSWER 19 OF 159 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 1998171523 MEDLINE
DOCUMENT NUMBER: 98171523 PubMed ID: 9502777
TITLE: Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats.
AUTHOR: Okuno A; Tamemoto H; Tobe K; Ueki K; Mori Y; Iwamoto K; Umesono K; Akanuma Y; Fujiwara T; Horikoshi H; Yazaki Y; Kadowaki T

CORPORATE SOURCE: Third Department of Internal Medicine, Faculty of Medicine,
University of Tokyo, Tokyo 113, Japan.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, **(1998 Mar 15)** 101 (6) 1354-61.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980430
Last Updated on STN: 20000303
Entered Medline: 19980423

AB Troglitazone (CS-045) is one of the thiazolidinediones that activate the peroxisome proliferator-activated receptor gamma (PPARgamma), which is expressed primarily in adipose tissues. To elucidate the mechanism by which troglitazone relieves insulin resistance in vivo, we studied its effects on the white adipose tissues of an obese animal model (obese Zucker rat). Administration of troglitazone for 15 d normalized mild hyperglycemia and marked hyperinsulinemia in these rats. Plasma triglyceride level was decreased by troglitazone in both obese and lean rats. Troglitazone did not change the total weight of white adipose tissues but increased the number of small adipocytes (< 2,500 micron2) approximately fourfold in both retroperitoneal and subcutaneous adipose tissues of obese rats. It also decreased the number of large adipocytes (> 5,000 micron2) by approximately 50%. In fact, the percentage of apoptotic nuclei was approximately 2.5-fold higher in the troglitazone-treated retroperitoneal white adipose tissue than control. Concomitantly, troglitazone normalized the expression levels of TNF-alpha which were elevated by 2- and 1.4-fold in the retroperitoneal and mesenteric white adipose tissues of the obese rats, respectively. Troglitazone also caused a dramatic decrease in the expression levels of **leptin**, which were increased by 4-10-fold in the white adipose tissues of obese rats. These results suggest that the primary action of troglitazone may be to increase the number of small adipocytes in white adipose tissues, presumably via PPARgamma. The increased number of small adipocytes and the decreased number of large adipocytes in white adipose tissues of troglitazone-treated obese rats appear to be an important mechanism by which increased expression levels of TNF-alpha and higher levels of plasma lipids are normalized, leading to alleviation of insulin resistance.

L4 ANSWER 20 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:62862 BIOSIS
DOCUMENT NUMBER: PREV199900062862
TITLE: Adipose tissue as an endocrine and paracrine organ.
AUTHOR(S): Mohamed-Ali, V.; Pinkney, J. H.; Coppack, S. W. (1)
CORPORATE SOURCE: (1) Dep. Med., Univ. Coll. London Sch. Med., Whittington Hosp., Archway Wing, Archway Rd., London N19 3UA UK
SOURCE: International Journal of Obesity, **(Dec., 1998)** Vol. 22, No. 12, pp. 1145-1158.
ISSN: 0307-0565.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB The discovery of **leptin** has imparted great impetus to adipose

tissue research by demonstrating a more active role for the adipocyte in energy regulation. Besides **leptin**, however, the adipose tissue also secretes a large number other signals. Cytokine signals, TNFalpha and IL-6, and components of the alternative pathway of complement influence peripheral fuel storage, mobilization and combustion, as well as energy homeostasis. In addition to the acute regulation of fuel metabolism, adipose tissue also influences steroid conversion and sexual maturation. In this way, adipose tissue is an active endocrine organ, influencing many aspects of fuel metabolism through a network of local and systemic signals, which interact with the established neuroendocrine regulators of adipose tissue. Thus, insulin, catecholamines and anterior pituitary endocrine axes interact at multiple levels with both cytokines and **leptin**. It may be proposed that the existence of this network of adipose tissue signalling pathways, arranged in an hierarchical fashion, constitutes a metabolic repertoire which enables the organism to adapt to a range of different metabolic challenges, including starvation, reproduction, times of physical activity, stress and infection, as well as short periods of gross energy excess. However, the occurrence of more prolonged periods of energy surplus, leading to obesity, is an unusual state in evolutionary terms, and the adipose tissue signalling repertoire, although sophisticated, adapts poorly to these conditions. Rather, the responses of the adipose tissue endocrine network to obesity are maladaptive, and lay the foundations of metabolic disease.

DUPLICATE 13

L4 ANSWER 21 OF 159 MEDLINE

ACCESSION NUMBER: 1999072340 MEDLINE
DOCUMENT NUMBER: 99072340 PubMed ID: 9856520

TITLE: High-flux dialysis lowers plasma **leptin** concentration in chronic dialysis patients.

AUTHOR: Coyne D W; Dagogo-Jack S; Klein S; Merabet E; Audrain J; Landt M
CORPORATE SOURCE: Department of Internal Medicine, Washington University School of Medicine, St Louis, MO 63110-1093, USA.. dcoyne@imgate.wustl.edu

SOURCE: AMERICAN JOURNAL OF KIDNEY DISEASES, **(1998 Dec)** 32 (6) 1031-5.
Journal code: 3H5; 8110075. ISSN: 1523-6838.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20010521
Entered Medline: 19990104

AB **Leptin** is a protein produced by fat cells and involved in body weight regulation. Plasma **leptin** is significantly higher in some hemodialysis (HD) patients than in normal controls. We examined the influence of dialyzer membrane biocompatibility and flux on elevated plasma **leptin** concentrations in hemodialysis patients. Employing a crossover design, **leptin** and **tumor** necrosis factor-alpha (TNF-alpha) levels were serially determined in eight chronic dialysis patients. Patients were dialyzed sequentially on low-flux cellulosic (TAF) dialyzers, low-flux (F8) polysulfone, high-flux (F80B)

polysulfone, then low-flux polysulfone and cellulosic dialyzers again. Mean **leptin** concentrations were similar when low-flux polysulfone or cellulosic dialyzers were employed (141.9+/-24.2 microg/L versus 137.8+/-18.4 microg/L, respectively (P=NS). In contrast, **leptin** fell significantly on the high-flux polysulfone dialyzer (99.4+/-16.2 microg/L) compared with cellulosic ($P < 0.005$), and low-flux polysulfone dialyzers ($P < 0.02$). **Leptin** clearance by the high-flux polysulfone dialyzer was significantly higher than the low-flux dialyzers (50.4+/-21.5 v -9.6+/-10.3 mL/min; P=0.043), but did not account fully for the 30% decline in plasma **leptin** during the high-flux arm of the study. Concentrations of TNF-alpha were lower when high-flux polysulfone dialyzers were employed, but there was no correlation of individual TNF-alpha levels with **leptin** concentrations. High-flux dialysis lowers plasma **leptin** concentrations an average of 30%, but biocompatibility does not influence **leptin** levels. The decrease in plasma **leptin** on high-flux dialysis cannot be explained solely by enhanced clearance.

DUPLICATE 14

L4 ANSWER 22 OF 159 MEDLINE

ACCESSION NUMBER: 1998318449 MEDLINE
DOCUMENT NUMBER: 98318449 PubMed ID: 9611147
TITLE: Endotoxin-induced alteration in the expression of **leptin** and beta3-adrenergic receptor in adipose tissue.
AUTHOR: Berkowitz D E; Brown D; Lee K M; Emala C; Palmer D; An Y; Breslow M
CORPORATE SOURCE: Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21287, USA.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, **(1998 Jun)** 274 (6 Pt 1) E992-7.
Journal code: 3U8; 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980817
Last Updated on STN: 20000303
Entered Medline: 19980806

AB Cytokines, such as **tumor** necrosis factor (TNF) and interleukin-6, may contribute to the anorexia and cachexia of infection, **cancer**, and AIDS. The present study tests the hypothesis that endotoxin alters the expression of two key fat cell proteins, **leptin** and beta3-adrenergic receptor (beta3-AR), through a mechanism involving TNF-alpha. Increasing doses of Escherichia coli endotoxin (lipopolysaccharide, LPS) resulted in dose-dependent elevations of plasma **leptin** (maximal response approximately 7-fold, half-maximal effective dose of approximately 16 microg/100 g body wt) and white fat **leptin** mRNA in C3/HeOUJ mice. LPS also produced a large decrease in adipose tissue beta3-AR mRNA and a parallel reduction in beta-agonist-induced activation of adenylyl cyclase. Changes in plasma **leptin** and beta3-AR mRNA were preceded by an approximately threefold increase in white fat TNF mRNA. TNF administration resulted in changes similar to those seen with LPS. We conclude that endotoxemia

results in an induction of **leptin** mRNA and a decrease in beta3-AR mRNA in adipose tissue, an effect that may be mediated by alterations in TNF-alpha.

DUPLICATE 15

L4 ANSWER 23 OF 159 MEDLINE
ACCESSION NUMBER: 1998426336 MEDLINE
DOCUMENT NUMBER: 98426336 PubMed ID: 9753498
TITLE: Gender-dependent alterations in serum **leptin** in alcoholic cirrhosis.
AUTHOR: McCullough A J; Bugianesi E; Marchesini G; Kalhan S C
CORPORATE SOURCE: Departments of Medicine and Pediatrics, Case Western Reserve University, Cleveland, Ohio, USA.
CONTRACT NUMBER: AA10445 (NIAAA)
SOURCE: GASTROENTEROLOGY, **(1998 Oct)** 115 (4) 947-53. Journal code: FH3; 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981029
Last Updated on STN: 20000303
Entered Medline: 19981022

AB BACKGROUND & AIMS: **Leptin** is a peptide that decreases food intake and increases energy expenditure. It is produced in fat cells, is stimulated by cytokines, and its levels in serum are higher in females. Because anorexia, hypermetabolism, and elevated cytokine levels are frequently observed in cirrhosis, we hypothesized that the serum **leptin** level would be elevated in cirrhosis. The aim of this study was to investigate the relationship of serum **leptin** to gender, body composition, and **tumor** necrosis factor (TNF). METHODS: Male (n = 18) and female (n = 10) abstinent alcoholic cirrhotic patients were studied and compared with control subjects (15 male and 8 female). Fat mass, fat-free body mass, and body cell mass were calculated by using H2[18O] and bromide dilution methodology. Serum **leptin** and TNF concentrations were measured by immunoassays. RESULTS: Fat mass was decreased only in male cirrhotics ($P < 0.05$), whereas body cell mass was decreased in both male and female cirrhotics ($P < 0.01$). **Leptin** levels were elevated in female ($P < 0.001$) but not male cirrhotics compared with controls. When expressed per kilogram of fat mass, **leptin** was elevated in both male ($P < 0.01$) and female ($P < 0.01$) cirrhotics. Women in both cirrhotic and control groups had higher **leptin** levels than men. TNF was elevated in both male and female cirrhotics and did not correlate with **leptin** levels. CONCLUSIONS: Cirrhotics have elevated serum **leptin** levels, which are related to both gender- and gender-dependent alterations in body composition.

DUPLICATE 16

L4 ANSWER 24 OF 159 MEDLINE
ACCESSION NUMBER: 1998399807 MEDLINE
DOCUMENT NUMBER: 98399807 PubMed ID: 9728091
TITLE: **Leptin** causes body weight loss in the absence of in vivo activities typical of cytokines of the IL-6 family.
AUTHOR: Agnello D; Meazza C; Rowan C G; Villa P; Ghezzi P; Senaldi G
CORPORATE SOURCE: "Mario Negri" Institute for Pharmacological Research, 20157

SOURCE: Milan, Italy.
AMERICAN JOURNAL OF PHYSIOLOGY, **(1998 Sep)** 275 (3 Pt 2) R913-9.
Journal code: 3U8; 0370511. ISSN: 0002-9513.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981008
Last Updated on STN: 20000303
Entered Medline: 19981001

AB To investigate if **leptin** shares in vivo activities with interleukin (IL)-6 family cytokines, it was tested in normal mice for the ability, after a single injection, to induce the acute-phase protein serum amyloid A, to potentiate the induction by IL-1 of serum corticosterone and IL-6, and to inhibit the induction by lipopolysaccharide of serum **tumor** necrosis factor and, after seven daily injections, to cause body weight loss and to change peripheral blood cell counts. At a 0.5 mg/kg dose, **leptin** caused body weight loss but did not show any of the other activities above. At a dose of 5 mg/kg, which also caused body weight loss, **leptin** potentiated the induction by IL-1 of serum corticosterone and IL-6 but did not show any other activity. In addition to causing body weight loss, **leptin** shows only some of the in vivo activities typical of IL-6 family cytokines and only if used at a dose that exceeds the one sufficient to affect body weight. In vivo, **leptin** seems to chiefly control body weight and not inflammatory or hematopoietic processes.

L4 ANSWER 25 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:492868 BIOSIS
DOCUMENT NUMBER: PREV199800492868
TITLE: Adipocyte: A secretory and endocrine cell.
AUTHOR(S): Ailhaud, Gerard (1)
CORPORATE SOURCE: (1) Cent. Biochim., CNRS UMR 6543, Lab. Biol. Dev. Tissu Adipeux, UNSA, Fac. Sci., Parc Valrose, 06108 Nice Cedex 2 France

SOURCE: M-S (Medecine Sciences), (**Aug.-Sept., 1998**) Vol. 14, No. 8-9, pp. 858-864.
ISSN: 0767-0974.

DOCUMENT TYPE: General Review
LANGUAGE: French
SUMMARY LANGUAGE: French

AB The concept that adipocytes are secretory cells has emerged over the past few years. Adipocytes synthesize and release a variety of peptide and non-peptide compounds, in addition to their ability to store and mobilize triglycerides, retinoids and cholesterol. These properties allow a cross-talk of white adipose tissue with other organs as well as within adipose tissue. The important finding that adipocytes secrete **leptin** as the product of ob gene has established adipose tissue as an endocrine organ which communicates with the central nervous system. **Tumor** necrosis factor-alpha secreted from adipocytes appears as an important component of insulin resistance in adipose tissue by decreasing the insulin receptor-signalling pathway. In vitro data on the secretion of mitogenic factors (IGF-I and lysophosphatidates) and adipogenic factors

(eicosanoids) and their effect on the proliferation and differentiation of preadipocytes to adipocytes suggest in vivo a cross-talk implicated in the hyperplastic development of adipose tissue.

DUPLICATE 17

L4 ANSWER 26 OF 159 MEDLINE
ACCESSION NUMBER: 1999071279 MEDLINE
DOCUMENT NUMBER: 99071279 PubMed ID: 9824605
TITLE: Elevated plasma **leptin** concentrations in early stages of experimental intestinal inflammation in rats.
AUTHOR: Barbier M; Cherbut C; Aube A C; Blottiere H M; Galmiche J P
CORPORATE SOURCE: Human Nutrition Research Centre, CRI-INSERM 95/08, CHU Hotel-Dieu, Nantes, France.
SOURCE: GUT, **(1998 Dec)** 43 (6) 783-90.
Journal code: FVT; 2985108R. ISSN: 0017-5749.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 20000303
Entered Medline: 19990126

AB BACKGROUND: Although **leptin**, an adipocyte derived hormone which regulates food intake and energy balance, is released after injections of **tumour** necrosis factor (TNF) and interleukin 1, plasma concentrations have not been characterised in chronic inflammation. **Leptin** may contribute to the anorexia and body weight loss associated particularly with the acute stages of inflammatory bowel disease. AIMS: To investigate plasma **leptin** concentrations during the time course of intestinal inflammation in different animal models. METHODS: Plasma **leptin** was measured at different time points in rats with trinitrobenzene sulphonic acid (TNBS) induced colitis, indomethacin induced ileitis, or endotoxic shock caused by lipopolysaccharide (LPS). Systemic TNF-alpha was also measured during acute inflammation. RESULTS: Plasma **leptin** concentrations increased fourfold eight hours after induction of TNBS colitis ($p<0.0001$) and twofold after administration of ethanol alone ($p<0.02$). Plasma **leptin** responses throughout the first post-treatment day were correlated with myeloperoxidase activity and gross damage scores. Similar **leptin** overexpression was observed in indomethacin induced ileitis and in rats with endotoxic shock. Plasma concentrations were lower in TNBS treated rats than in controls on day 5 before reaching a similar concentration on day 14. Anorexia and body weight loss were observed during the first four days post-TNBS. A significant increase in systemic TNF-alpha was only detected in LPS treated rats. CONCLUSION: Elevated plasma **leptin** concentrations, correlated with the degree of inflammation and associated with anorexia, were induced in rats during the early stages of experimental intestinal inflammation but proved transient; this might account for discrepancies in recent results concerning concentrations in patients with inflammatory bowel diseases.

DUPLICATE 18

L4 ANSWER 27 OF 159 MEDLINE
ACCESSION NUMBER: 1998387756 MEDLINE
DOCUMENT NUMBER: 98387756 PubMed ID: 9722301
TITLE: Expression of the **leptin** receptor in human leukaemic blast cells.
AUTHOR: Nakao T; Hino M; Yamane T; Nishizawa Y; Morii H; Tatsumi N
CORPORATE SOURCE: Department of Clinical Haematology, Osaka City University Medical School, Osaka, Japan.
SOURCE: BRITISH JOURNAL OF HAEMATOLOGY, **(1998 Aug)** 102 (3) 740-5.
Journal code: AXC; 0372544. ISSN: 0007-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981020
Last Updated on STN: 19981020
Entered Medline: 19981007

AB The **leptin** receptor is a member of the cytokine receptor superfamily, and is expressed in CD34 haemopoietic stem cells. We examined expression of the **leptin** receptor in fresh human leukaemia cells. Northern blot analysis showed the **leptin** receptor was expressed in leukaemic cells from patients with acute myeloblastic leukaemia, acute lymphoblastic leukaemia and chronic myeloid leukaemia (CML). In CML, higher expression was observed in blast crisis than in chronic phase. The expression of **leptin** receptor decreased during in vitro differentiation of leukaemic blast cells. It appeared that expression of the **leptin** receptor was associated with immature leukaemic blast cells. Our findings may indicate the possibility that **leptin** has some role in leukaemia.

DUPLICATE 19

L4 ANSWER 28 OF 159 MEDLINE
ACCESSION NUMBER: 1998215223 MEDLINE
DOCUMENT NUMBER: 98215223 PubMed ID: 9555938
TITLE: Adipose tissue ob mRNA expression in humans: discordance with plasma **leptin** and relationship with adipose TNFalpha expression.
AUTHOR: Ranganathan S; Maffei M; Kern P A
CORPORATE SOURCE: Department of Medicine, University of Arkansas for Medical Sciences and the John L. McClellan VA Medical Center, Little Rock 72205, USA.
CONTRACT NUMBER: DK 39176 (NIDDK)
SOURCE: JOURNAL OF LIPID RESEARCH, **(1998 Apr)** 39 (4) 724-30.
Journal code: IX3; 0376606. ISSN: 0022-2275.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980618
Last Updated on STN: 20000303
Entered Medline: 19980611

AB Elevated plasma **leptin** levels are found in obese humans, suggesting a defect in the function of **leptin** in regulating body

weight and adiposity. In 53 subjects covering a broad range of adiposity, we examined the relationships between plasma **leptin**, adipose tissue ob mRNA levels, and adipose tissue TNF mRNA. There was a highly significant correlation between plasma **leptin** levels and every index of adiposity. In contrast, the relationship between ob mRNA levels and adiposity was weak. Adipose tissue from obese subjects demonstrated higher ob mRNA levels than adipose tissue from lean subjects (lean: 0.49+/-0.05; obese 0.87+/-0.09 arbitrary units, P< 0.05). However, there was no significant correlation between body fat and ob mRNA level. In addition, there was no significant relationship between ob mRNA levels and plasma **leptin** levels, which were measured in the same subjects. In addition to the measure of ob mRNA levels, adipose TNF mRNA levels were measured in 18 subjects. TNF mRNA levels varied with ob mRNA levels (r = 0.44, P = 0.06). These data show that plasma **leptin** levels are not directly related to adipose tissue ob mRNA levels, suggesting posttranscriptional regulation of **leptin** expression, either at the level of the adipocyte, or by alteration of plasma **leptin** degradation or clearance. In addition, the parallel changes in ob and TNF mRNA in adipose tissue suggest that these two important factors in the defense against obesity may be regulated similarly.

DUPLICATE 20

L4 ANSWER 29 OF 159 MEDLINE

ACCESSION NUMBER: 1999179640 MEDLINE
DOCUMENT NUMBER: 99179640 PubMed ID: 10079904
TITLE: Nutrition in inflammatory bowel disease.
AUTHOR: Murch S H; Walker-Smith J A
CORPORATE SOURCE: University Department of Paediatric Gastroenterology, Royal Free Hospital, London, UK.
SOURCE: BAILLIERES CLINICAL GASTROENTEROLOGY, **(1998 Dec)** 12 (4) 719-38. Ref: 86
Journal code: BBG; 8704786. ISSN: 0950-3528.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990517
Last Updated on STN: 19990517
Entered Medline: 19990430

AB Nutrition is clearly disturbed by active intestinal inflammation. Appetite is reduced, yet energy substrates are diverted into the inflammatory process, and thus weight loss is characteristic. The nutritional disturbance represents part of a profound defect of somatic function. Linear growth and pubertal development in children are notably retarded, body composition is altered, and there may be significant psychosocial disturbance. Macrophage products such as **tumour** necrosis factor-alpha and interleukins-1 and 6 may be the central molecules that link the inflammatory process to this derangement of homeostasis. Intriguingly, there is also increasing evidence that an aggressive nutritional programme may in itself be sufficient to reduce the mucosal inflammatory response. Recent evidence suggests that enteral nutrition alone may reduce many pro-inflammatory cytokines to normal and allow

mucosal healing. In addition, specific nutritional components, such as n-3 polyunsaturated fatty acids, may have an anti-inflammatory effect as they may alter the pattern of leukotrienes generated during the immune response. The recent discovery of the specific molecular mediators of appetite and body composition, such as **leptin** and myostatin, may allow increased therapeutic specificity and further improvement in the nutritional treatment of the inflammatory bowel diseases.

DUPLICATE 21

L4 ANSWER 30 OF 159 MEDLINE
ACCESSION NUMBER: 1998379177 MEDLINE
DOCUMENT NUMBER: 98379177 PubMed ID: 9713555
TITLE: The circadian rhythm of **leptin** is preserved in growth hormone deficient hypopituitary adults.
AUTHOR: Kousta E; Chrisoulidou A; Lawrence N J; al-Shoumer K A; Parker K H; McCarthy M I; Johnston D G
CORPORATE SOURCE: Unit of Metabolic Medicine, Imperial College School of Medicine, St. Mary's Hospital, London, UK..
e.kousta@ic.ac.uk
SOURCE: CLINICAL ENDOCRINOLOGY, **(1998 Jun)** 48 (6) 685-90.
Journal code: DCI; 0346653. ISSN: 0300-0664.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980903
Last Updated on STN: 20000303
Entered Medline: 19980827

AB OBJECTIVE: **Leptin** acts as a satiety factor in regulating food intake and body homeostasis, but its regulation is not well defined. Specific **leptin** receptors have been found in the brain and it has been hypothesized that **leptin** production by adipose tissue is under neuroendocrine control. A circadian rhythm has been demonstrated with highest **leptin** levels between midnight and early morning hours. The possibility that hypopituitarism (or pituitary surgery +/- radiotherapy) abolishes this **leptin** rhythm was investigated by measuring serum **leptin** levels during a 24-h period in patients with impaired pituitary function. PATIENTS AND DESIGN: Circulating **leptin** levels were measured hourly over 24-h in 14 hypopituitary patients (8 women and 6 men) using a sensitive and specific radioimmunoassay. Hypopituitarism was the consequence of pituitary **tumors** treated surgically and/or with radiotherapy. All patients were GH deficient and were receiving conventional replacement with cortisol (n = 13), thyroxine (n = 12) and desmopressin (n = 4) but not with GH. RESULTS: A significant diurnal variation in circulating **leptin** concentrations was observed in 13 of the 14 patients. The mean (+/- SEM) **leptin** levels for 8 women were 51.9 (+/- 10.7) ng/ml and for 6 men 11.0 (+/- 2.0) micrograms/l. The overall lowest **leptin** levels (29.3 +/- 7.9 ng/ml) were observed at 0830 h after overnight fasting, rising gradually to maximum levels (43.0 +/- 9.8 ng/ml) at 0200 h declining thereafter towards fasting values. The mean (+/- SEM) magnitude of circadian variation in absolute **leptin** levels from the calculated mean level for each patient was 5.6 (+/- 1.2) ng/ml (8.4 +/- 1.4 for women and 1.9 +/- 0.3 for men). The mean (+/- SEM) of the ratio of the amplitude versus mean **leptin** levels over 24 h for each individual patient was 0.18 (+/- 0.02) (0.19 +/- 0.03 for women and

0.18 +/- 0.02 for men). CONCLUSIONS: A circadian rhythm for **leptin** is generally present in hypopituitary patients who had undergone pituitary surgery and/or radiotherapy, with the highest serum **leptin** levels being obtained between midnight and early morning hours. Although some patients had some residual pituitary activity, intact hypothalamic-pituitary function is not essential for **leptin**'s circadian rhythm.

DUPLICATE 22

L4 ANSWER 31 OF 159 MEDLINE

ACCESSION NUMBER: 1998289588 MEDLINE
DOCUMENT NUMBER: 98289588 PubMed ID: 9618269
TITLE: **Leptin** regulation of peroxisome proliferator-activated receptor-gamma, **tumor** necrosis factor, and uncoupling protein-2 expression in adipose tissues.
AUTHOR: Qian H; Hausman G J; Compton M M; Azain M J; Hartzell D L; Baile C A
CORPORATE SOURCE: Department of Foods and Nutrition, University of Georgia, Athens 30602, USA.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1998 May 29)** 246 (3) 660-7.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980716
Last Updated on STN: 20000303
Entered Medline: 19980702

AB It has previously been reported that intracerebroventricular (i.c.v.) administration of **leptin** induced adipose tissue apoptosis in addition to influencing lipid metabolism. The objective of the present study was to determine if the expressions of peroxisome proliferator-activated receptor-gamma (PPAR gamma), uncoupling protein-2 (UCP2), and **tumor** necrosis factor (TNF alpha) were influenced by in vivo **leptin** treatment. Expression of PPAR gamma, UCP2, and TNF alpha in epididymal fat tissue was examined by Western immunoblot and in situ immunocytochemical analysis after 5 days of i.c.v. **leptin** treatment. Young and old rats (3 and 8 months old) were treated with or without 5 micrograms/d **leptin**. **Leptin** treatment increased PPAR gamma expression by 70-80% ($P < 0.01$) in both age groups. **Leptin** treatment decreased the expression of UCP2 ($P < 0.01$) in young rats, whereas it increased UCP2 expression ($P < 0.01$) in old rats. **Leptin** treatment also decreased TNF alpha expression by 40% ($P < 0.01$) in young rats but did not influence its expression in old rats. The basal level of expression of PPAR gamma was greater in 3-month-old rats than in 8-month-old rats. The basal level of UCP2 and TNF alpha expression was not different between the two age groups. These immunoblotting data were further confirmed by in situ immunocytochemical analysis. The present study suggests that expression of PPAR gamma may be directly involved in the **leptin**-induced adipocyte apoptosis signal pathway, whereas UCP2 and TNF alpha may play roles in the **leptin**-induced lipolysis process.

DUPLICATE 23

L4 ANSWER 32 OF 159 MEDLINE
ACCESSION NUMBER: 1998128709 MEDLINE
DOCUMENT NUMBER: 98128709 PubMed ID: 9467580
TITLE: Determinants of serum **leptin** levels in Cushing's syndrome.
AUTHOR: Widjaja A; Schurmeyer T H; Von zur Muhlen A; Brabant G
CORPORATE SOURCE: Department of Clinical Endocrinology, Medizinische Hochschule Hannover, Germany.
SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, **(1998 Feb)** 83 (2) 600-3.
Journal code: HRB; 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980312
Last Updated on STN: 20000303
Entered Medline: 19980227

AB Corticosteroids and insulin increase **leptin** expression in vivo and in vitro. To investigate whether increased serum cortisol influences serum **leptin** concentrations in humans, we analyzed fasting serum **leptin** and insulin levels in 50 patients with Cushing's syndrome [34 female patients: 27 with the pituitary form and 7 with the adrenal form; age, 41.6 +/- 2.7 yr; body mass index (BMI), 29.6 +/- 1.2 kg/m2; 16 male patients all with the pituitary form; age, 39.2 +/- 3.1 yr; BMI, 26.3 +/- 2.3 kg/m2] and in controls matched for BMI, age, and gender. Serum **leptin** levels were higher in female than in male patients in both the Cushing ($P < 0.01$) and control ($P < 0.001$) groups. Disease-specific differences in serum **leptin** levels were only detected in male (106 vs. 67 pmol/L; Cushing's syndrome vs. control, $P < 0.05$), not female, patients. Multiple stepwise regression analysis of both patient groups revealed insulin as the best predictor of serum **leptin** concentrations, accounting for 37% of the variance in serum **leptin** levels, in contrast to BMI or mean serum cortisol (as measured by sampling in 10-min intervals over 24 h). In the subgroup of patients (n = 9) with pituitary adenoma, serum **leptin** levels were reduced after **tumor** resection, with concurrent decreases in serum cortisol, insulin, and BMI. In conclusion, chronic hypercortisolemia in Cushing's syndrome appears not to directly affect serum **leptin** concentrations, but to have an indirect effect via the associated hyperinsulinemia and/or impaired insulin sensitivity.

L4 ANSWER 33 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:524573 BIOSIS
DOCUMENT NUMBER: PREV199800524573
TITLE: Fat tissue, TNF-alpha, insulin, and insulin sensitivity: The regulation of plasma **leptin** in heart failure patients.
AUTHOR(S): Anker, S. D. (1); Leyva, F. (1); Egerer, K. R.; Godsland, K. R.; Niebauer, J. (1); Kox, W. J.; Poole-Wilson, P. A. (1); Coats, A. J. S. (1)
CORPORATE SOURCE: (1) Cardiac Med., NHLI, London UK
SOURCE: European Heart Journal, (**Aug., 1998**) Vol. 19, No. ABST. SUPPL., pp. 592.

Meeting Info.: XXth Congress of the European Society of Cardiology Vienna, Austria August 22-26, 1998 European Society of Cardiology
. ISSN: 0195-668X.

DOCUMENT TYPE: Conference
LANGUAGE: English

DUPLICATE 24

L4 ANSWER 34 OF 159 MEDLINE
ACCESSION NUMBER: 1998099791 MEDLINE
DOCUMENT NUMBER: 98099791 PubMed ID: 9435324
TITLE: Transplantable rat glucagonomas cause acute onset of severe anorexia and adipsia despite highly elevated NPY mRNA levels in the hypothalamic arcuate nucleus.
AUTHOR: Jensen P B; Blume N; Mikkelsen J D; Larsen P J; Jensen H I; Holst J J; Madsen O D
CORPORATE SOURCE: Hagedorn Research Institute, 2820 Gentofte, Copenhagen, Denmark.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, **(1998 Jan 15)** 101 (2) 503-10.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980217
Last Updated on STN: 19980217
Entered Medline: 19980205

AB We have isolated a stable, transplantable, and small glucagonoma (MSL-G-AN) associated with abrupt onset of severe anorexia occurring 2-3 wk after subcutaneous transplantation. Before onset of anorexia, food consumption is comparable to untreated controls. Anorexia is followed by adipsia and weight loss, and progresses rapidly in severity, eventually resulting in reduction of food and water intake of 100 and 80%, respectively. During the anorectic phase, the rats eventually become hypoglycemic and hypothermic. The **tumor**-associated anorexia shows no sex difference, and is not affected by bilateral abdominal vagotomy, indicating a direct central effect. The adipose satiety factor **leptin**, known to suppress food intake by reducing hypothalamic neuropeptide Y (NPY) levels, was not found to be expressed by the **tumor**, and circulating **leptin** levels were reduced twofold in the anorectic phase. A highly significant increase in hypothalamic (arcuate nucleus) NPY mRNA levels was found in anorectic rats compared with control animals. Since elevated hypothalamic NPY is among the most potent stimulators of feeding and a characteristic of most animal models of hyperphagia, we conclude that the MSL-G-AN glucagonoma releases circulating factor(s) that overrides the hypothalamic NPY-ergic system, thereby eliminating the orexigenic effect of NPY. We hypothesize a possible central role of proglucagon-derived peptides in the observed anorexia.

DUPLICATE 25

L4 ANSWER 35 OF 159 MEDLINE
ACCESSION NUMBER: 1998347591 MEDLINE
DOCUMENT NUMBER: 98347591 PubMed ID: 9682669

TITLE: Plasma **leptin** in chronic inflammatory bowel disease and HIV: implications for the pathogenesis of anorexia and weight loss.

AUTHOR: Ballinger A; Kelly P; Hallyburton E; Besser R; Farthing M

CORPORATE SOURCE: Digestive Diseases Research Centre, St Bartholomew's, London, U.K.

SOURCE: CLINICAL SCIENCE, **(1998 May)** 94 (5) 479-83. Journal code: DIZ; 7905731. ISSN: 0143-5221.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199808

ENTRY DATE: Entered STN: 19980817
Last Updated on STN: 20000303
Entered Medline: 19980803

AB 1. **Leptin** inhibits food intake and is an important regulator of long-term energy balance. In rodents, plasma concentrations of **leptin** are increased by administration of interleukin-1 and **tumour** necrosis factor. Hyperleptinaemia may mediate the anorexia and weight loss which is observed in chronic infections and inflammatory conditions. 2. Plasma **leptin** and soluble **tumour** necrosis factor receptor (sTNF-r55) concentrations were measured in patients with inflammatory bowel disease and acquired immunodeficiency syndrome (AIDS), and healthy controls. 3. The patients with AIDS were severely wasted [% body fat 12 (9-16); median (interquartile range)] compared with those with inflammatory bowel disease [25.1 (19-31.5)] and control subjects [29.4 (23.6-37.8)]. **Leptin** concentrations were highly correlated with percentage body fat in controls ($r = 0.74$, $P < 0.001$) and patients with IBD ($r = 0.73$, $P < 0.001$) but not in the patients with AIDS ($r = -0.024$). **Leptin** concentrations were similar in the inflammatory bowel disease [4.8 (2.6-10.1) ng/ml] and control groups [8.0 (3.1-14.1) ng/ml] but were significantly lower ($P < 0.05$) in patients with AIDS [1.8 (1.5-2.3) ng/ml] after 23 patients were matched for sex and percentage body fat in patients with inflammatory bowel disease [2.4 (1.8-4.1) ng/ml]. Plasma concentrations of sTNF-r55 were higher in both the patients with inflammatory bowel disease [0.19 (0.16-0.23) ng/ml] and those with AIDS [4.8 (2.8-7.3) ng/ml] compared with controls [0.14 (0.09-0.16) ng/ml] but were not correlated with either percentage body fat or plasma **leptin** concentrations. 4. Hyperleptinaemia does not appear to mediate the anorexia and weight loss associated with inflammatory bowel disease and AIDS. In patients with AIDS with extreme wasting there was no relationship between body fat and **leptin** and this may be related to the rapid weight loss which occurs in these patients.

L4 ANSWER 36 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1999:112338 BIOSIS

DOCUMENT NUMBER: PREV199900112338

TITLE: Regulation of **leptin** production: A dominant role for the sympathetic nervous system.

AUTHOR(S): Trayhurn, Paul (1); Duncan, Jacqueline S.; Hoggard, Nigel; Rayner, D. Vernon

CORPORATE SOURCE: (1) Mol. Physiol. Group, Div. Biomed. Sci., Rowett Res.

SOURCE: Inst., Bucksburn, Aberdeen AB21 9SB UK
Proceedings of the Nutrition Society, (**Aug., 1998**
) Vol. 57, No. 3, pp. 413-419.
Meeting Info.: Joint Meeting of the Nutrition Society and the Association for the Study of Obesity London, England, UK February 18, 1998 The Association for the Study of Obesity
. ISSN: 0029-6651.

DOCUMENT TYPE: Conference
LANGUAGE: English

DUPLICATE 26

L4 ANSWER 37 OF 159 MEDLINE
ACCESSION NUMBER: 1998330467 MEDLINE
DOCUMENT NUMBER: 98330467 PubMed ID: 9664082
TITLE: Obesity and diabetes in TNF-alpha receptor- deficient mice.
AUTHOR: Schreyer S A; Chua S C Jr; LeBoeuf R C
CORPORATE SOURCE: Department of Medicine, University of Washington, Seattle, Washington 98195, USA.
CONTRACT NUMBER: DK47473 (NIDDK)
HL07247 (NHLBI)
HL52848 (NHLBI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, **(1998 Jul 15)** 102 (2) 402-11.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980828
Last Updated on STN: 19990129
Entered Medline: 19980820

AB TNF-alpha may play a role in mediating insulin resistance associated with obesity. This concept is based on studies of obese rodents and humans, and cell culture models. TNF elicits cellular responses via two receptors called p55 and p75. Our purpose was to test the involvement of TNF in glucose homeostasis using mice lacking one or both TNF receptors. C57BL/6 mice lacking p55 (p55(-)/-), p75, (p75(-)/-), or both receptors (p55(-)/-p75(-)/-) were fed a high-fat diet to induce obesity. Marked fasting hyperinsulinemia was seen for p55(-)/-p75(-)/- males between 12 and 16 wk of feeding the high-fat diet. Insulin levels were four times greater than wild-type mice. In contrast, p55(-)/- and p75(-)/- mice exhibited insulin levels that were similar or reduced, respectively, as compared with wild-type mice. In addition, high-fat diet-fed p75(-)/- mice had the lowest body weights and **leptin** levels, and improved insulin sensitivity. Obese (db/db) mice, which are not responsive to **leptin**, were used to study the role of p55 in severe obesity. Male p55(-)/-db/db mice exhibited threefold higher insulin levels and twofold lower glucose levels at 20 wk of age than control db/db expressing p55. All db/db mice remained severely insulin resistant based on fasting plasma glucose and insulin levels, and glucose and insulin tolerance tests. Our data do not support the concept that TNF, acting via its receptors, is a major contributor to obesity-associated insulin resistance. In fact, data suggest that the two TNF receptors work in concert to protect against

diabetes.

DUPLICATE 27

L4 ANSWER 38 OF 159 MEDLINE
ACCESSION NUMBER: 1999001115 MEDLINE
DOCUMENT NUMBER: 99001115 PubMed ID: 9784936
TITLE: **Leptin**: physiology and pathophysiology.
AUTHOR: Fruhbeck G; Jebb S A; Prentice A M
CORPORATE SOURCE: MRC Dunn Clinical Nutrition Centre, Cambridge, UK.
SOURCE: CLINICAL PHYSIOLOGY, **(1998 Sep)** 18 (5) 399-419.
Ref: 155
Journal code: DKG; 8309768. ISSN: 0144-5979.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981229

AB The identification and sequencing of the ob gene and its product, **leptin**, in late 1994 opened new insights in the study of the mechanisms controlling body weight and led to a surge of research activity. During this time, a considerable body of knowledge regarding **leptin**'s actions has been accumulated and the field continues to expand rapidly. Currently there is particular interest in the interaction of **leptin** with other peripheral and neural mechanisms to regulate body weight, reproduction and immunological response. In this review, we attempt to place the current state of knowledge about **leptin** in the broader perspective of physiology, including its structural characteristics, receptors, binding proteins, signalling pathways, regulation of adipose tissue expression and production, secretion patterns, clearance mechanisms and functional effects. In addition, **leptin**'s involvement in the pathophysiology of obesity, anorexia nervosa, diabetes mellitus, polycystic ovary syndrome, acquired immunodeficiency syndrome, **cancer**, nephropathy, thyroid disease, Cushing's syndrome and growth hormone deficiency will be reviewed.

DUPLICATE 28

L4 ANSWER 39 OF 159 MEDLINE
ACCESSION NUMBER: 1999074433 MEDLINE
DOCUMENT NUMBER: 99074433 PubMed ID: 9852241
TITLE: Gram-negative and gram-positive bacterial products induce differential cytokine profiles in the brain: analysis using an integrative molecular-behavioral in vivo model.
AUTHOR: Plata-Salaman C R; Ilyin S E; Gayle D; Flynn M C
CORPORATE SOURCE: Division of Molecular Biology, School of Life and Health Sciences, University of Delaware, Newark, Delaware 19716-2590, USA.
SOURCE: INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE, **(1998 Feb)** 1 (2) 387-97.
Journal code: C8H; 9810955. ISSN: 1107-3756.
PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990402
Last Updated on STN: 20000303
Entered Medline: 19990322

AB Bacterial-derived products [e.g., lipopolysaccharide (LPS) from Gram-negative and muramyl dipeptide (MDP) from Gram-positive bacteria] are proposed to play a pivotal role in the generation of neurological and neuroinflammatory/immunological responses during bacterial infections of the nervous system. LPS and MDP may act through cytokines; cytokine-neuropeptide interactions may also be involved. Here, we investigated cytokine and neuropeptide mRNA profiles in specific brain regions in response to the intracerebroventricular administration of LPS and MDP. IL-beta1 system components (ligand, signalling receptor, receptor accessory proteins, receptor antagonist), TNF-alpha, TGF-beta1, glycoprotein 130 (IL-6 receptor signal transducer), **OB protein** (**leptin**) receptor, neuropeptide Y, Y5 receptor, and pro-opiomelanocortin (opioid peptide precursor) mRNAs were analyzed. The same brain region sample was assayed for all components. LPS and MDP administration induced significantly different behavioral and molecular profiles. LPS was significantly more potent than MDP in inducing anorexia and in up-regulating pro-inflammatory cytokines (IL- beta1 and TNF-alpha mRNAs in the cerebellum, hippocampus and hypothalamus; MDP was more potent in up-regulating anti-inflammatory cytokine (IL-1 receptor antagonist and TGF-beta1) mRNAs. LPS and MDP also modulated hypothalamic IL-1 receptor mRNA components, but did not affect any of the neuropeptide-related components examined. The results suggest that the magnitude of neurological manifestations induced by LPS and MDP may involve the ratio between stimulatory and inhibitory cytokines, and this ratio may have implications for the neuroinflammatory/neurotoxic events associated with bacterial infections of the central nervous system.

L4 ANSWER 40 OF 159 MEDLINE DUPLICATE 29
ACCESSION NUMBER: 1998250971 MEDLINE
DOCUMENT NUMBER: 98250971 PubMed ID: 9589084
TITLE: Growth and endocrinological disorders up to 21 years after treatment for acute lymphoblastic **leukemia** in childhood.
AUTHOR: Birkebaek N H; Fisker S; Clausen N; Tuovinen V; Sindet-Pedersen S; Christiansen J S
CORPORATE SOURCE: Department of Pediatrics, University Hospital of Aarhus at Skejby, Denmark.
SOURCE: MEDICAL AND PEDIATRIC ONCOLOGY, **(1998 Jun)** 30 (6) 351-6.
Journal code: M6P; 7506654. ISSN: 0098-1532.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980609
Last Updated on STN: 19980609
Entered Medline: 19980528

AB BACKGROUND: Our aim was to evaluate endocrinological status 10-21 years after treatment for childhood acute lymphoblastic **leukemia** (ALL) with chemotherapy (C) and cranial irradiation (C + I) or only C, and to

correlate the endocrine data with growth parameters. PROCEDURE: Of 30 patients (15 females and 15 males), 18 were treated with C + I and 12 were treated with C only. Height standard deviation score (HSDS) and body mass index standard deviation score (BMISDS) before treatment, at end of treatment, and at follow-up were calculated from height and weight registered from the charts. At follow-up examinations, provocative growth hormone (GH) tests (clonidine and insulin tolerance test) and an ACTH test were performed. Furthermore, blood samples for hormonal analysis, IGF-I, IGFBP-3, GHBP, and **leptin** were drawn. RESULTS: Eleven patients (9 treated with C + I and 2 treated with C) showed insufficient response to GH tests. Two patients had hypogonadism. HSDS and IGF-I were significantly lower and GHBP significantly higher in GH-deficient patients compared to the group with normal GH secretion at follow-up. BMISDS steadily increased from start of treatment until follow-up, independent of GH status at follow-up. BMISDS at follow-up was positively correlated with serum **leptin** ($P < 0.001$), and serum **leptin** was significantly higher in the cranial irradiated group as compared to the nonirradiated group. CONCLUSIONS: GH deficiency is frequently found at long-term follow-up in patients treated for childhood ALL. Other hormonal deficiencies are rare. HSDS at long-term follow-up is dependent on GH secretory status. Long-term endocrinological follow-up examinations in patients treated for childhood ALL are recommended, as hormonal replacement therapy may be indicated.

L4 ANSWER 41 OF 159 MEDLINE DUPLICATE 30

ACCESSION NUMBER: 1999001216 MEDLINE
DOCUMENT NUMBER: 99001216 PubMed ID: 9785037
TITLE: Hypothalamic control of gonadotropin secretion by LHRH, FSHRF, NO, cytokines, and **leptin**.
AUTHOR: McCann S M; Kimura M; Walczewska A; Karanth S; Rettori V; Yu W H
CORPORATE SOURCE: Pennington Biomedical Research Center, Louisiana State University, Baton Rouge 70808-4124, USA.
CONTRACT NUMBER: DK4390 (NIDDK)
MH51853 (NIMH)
SOURCE: DOMESTIC ANIMAL ENDOCRINOLOGY, **(1998 Sep)** 15 (5) 333-44. Ref: 53
Journal code: DO1; 8505191. ISSN: 0739-7240.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981230

AB Gonadotropin secretion by the pituitary gland is under the control of luteinizing hormone-releasing hormone (LHRH) and the putative follicle stimulating hormone-releasing factor (FSHRF). Lamprey III LHRH is a potent FSHRF in the rat and seems to be resident in the FSH controlling area of

the rat hypothalamus. It is an analog of mammalian LHRH and may be the long sought FSHRF. Gonadal steroids feedback at hypothalamic and pituitary levels to either inhibit or stimulate the release of LH and FSH, which is also affected by inhibin and activin secreted by the gonads. Important control is exercised by acetylcholine, norepinephrine (NE), dopamine, serotonin, melatonin, and glutamic acid (GA). Furthermore, LH and FSH also act at the hypothalamic level to alter secretion of gonadotropins. More recently, growth factors have been shown to have an important role. Many peptides act to inhibit or increase release of LH and the sign of their action is often reversed by estrogen. A number of cytokines act at the hypothalamic level to suppress acutely the release of LH but not FSH. NE, GA, and oxytocin stimulate LHRH release by activation of neural nitric oxide synthase (nNOS). The pathway is as follows: oxytocin and/or GA activate NE neurons in the medial basal hypothalamus (MBH) that activate NOergic neurons by alpha, (alpha 1) receptors. The NO released diffuses into LHRH terminals and induces LHRH release by activation of guanylate cyclase (GC) and cyclooxygenase. NO not only controls release of LHRH bound for the pituitary, but also that which induces mating by actions in the brain stem. An exciting recent development has been the discovery of the adipocyte hormone, **leptin**, a cytokine related to **tumor** necrosis factor (TNF) alpha. In the male rat, **leptin** exhibits a high potency to stimulate FSH and LH release from hemipituitaries incubated in vitro, and increases the release of LHRH from MBH explants. LHRH and **leptin** release LH by activation of NOS in the gonadotropes. The NO released activates GC that releases cyclic GMP, which induces LH release. **Leptin** induces LH release in conscious, ovariectomized estrogen-primed female rats, presumably by stimulating LHRH release. At the effective dose of estrogen to activate LH release, FSH release is inhibited. **Leptin** may play an important role in induction of puberty and control of LHRH release in the adult as well.

L4 ANSWER 42 OF 159 MEDLINE DUPLICATE 31

ACCESSION NUMBER:	1999001214 MEDLINE
DOCUMENT NUMBER:	99001214 PubMed ID: 9785035
TITLE:	Immune and endocrine regulation of food intake in sick animals.
AUTHOR:	Johnson R W
CORPORATE SOURCE:	Department of Animal Sciences, University of Illinois, Urbana 61801, USA.
CONTRACT NUMBER:	DK49311 (NIDDK) DK51576 (NIDDK)
SOURCE:	DOMESTIC ANIMAL ENDOCRINOLOGY, **(1998 Sep)** 15 (5) 309-19. Ref: 81 Journal code: DO1; 8505191. ISSN: 0739-7240.
PUB. COUNTRY:	United States
	Journal; Article; (JOURNAL ARTICLE)
	General Review; (REVIEW)
	(REVIEW, TUTORIAL)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	199812
ENTRY DATE:	Entered STN: 19990115 Last Updated on STN: 20000303

Entered Medline: 19981230

AB To understand why sick animals do not eat, investigators have studied how the immune system interacts with the central nervous system (CNS), where motivation to eat is ultimately controlled. The focus has been on the cytokines secreted by activated mononuclear myeloid cells, which include interleukin-1 beta (IL-1 beta), interleukin-6 (IL-6), and **tumor** necrosis factor-alpha (TNF-alpha). Either central or peripheral injection of recombinant IL-1 beta, IL-6, and TNF-alpha reduce food-motivated behavior and food intake in rodents. Moreover, these cytokines and their receptors are present in the endocrine system and brain, and antagonism of this system (i.e., the cytokine network) has been shown to block or abrogate anorexia induced by inflammatory stimuli. Recent studies indicate that the same cytokines act on adipocytes and induce secretion of **leptin**, a protein whose activity has been neuroanatomically mapped to brain areas involved in regulating food intake and energy expenditure. Therefore, many findings converge to suggest that the reduction of food intake in sick animals is mediated by inflammatory cytokines, which convey a message from the immune system to the endocrine system and CNS. The nature of this interaction is the focus of this short review.

L4 ANSWER 43 OF 159 MEDLINE DUPLICATE 32

ACCESSION NUMBER: 1998365321 MEDLINE
DOCUMENT NUMBER: 98365321 PubMed ID: 9688632
TITLE: Advancing age and insulin resistance: role of plasma **tumor** necrosis factor-alpha.
AUTHOR: Paolisso G; Rizzo M R; Mazziotti G; Tagliamonte M R; Gambardella A; Rotondi M; Carella C; Giugliano D; Varricchio M; D'Onofrio F
CORPORATE SOURCE: Department of Geriatric Medicine and Metabolic Diseases, University of Napoli, 80138 Naples, Italy.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, **(1998 Aug)** 275 (2 Pt 1) E294-9.
Journal code: 3U8; 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980925
Last Updated on STN: 20000303
Entered Medline: 19980916

AB In 70 healthy subjects with a large age range, the relationships between plasma **tumor** necrosis factor-alpha (TNF-alpha) and body composition, insulin action, and substrate oxidation were investigated. In the cross-sectional study (n = 70), advancing age correlated with plasma TNF-alpha concentration (r = 0.64, P < 0.001) and whole body glucose disposal (WBGD; r= -0.38, P < 0.01). The correlation between plasma TNF-alpha and age was independent of sex and body fat (BF; r = 0.31, P < 0.01). Independent of age and sex, a significant relationship between plasma TNF-alpha and **leptin** concentration (r = 0.29, P < 0.02) was also found. After control for age, sex, BF, and waist-to-hip ratio (WHR), plasma TNF-alpha was still correlated with WBGD (r = -0.33, P < 0.007). Further correction for plasma free fatty acid (FFA) concentration made the latter correlation no more significant. In a multivariate

analysis, a model made by age, sex, BF, fat- free mass, WHR, and plasma TNF-alpha concentrations explained 69% of WBGD variability with age ($P < 0.009$), BF ($P < 0.006$), fat-free mass ($P < 0.005$), and plasma TNF-alpha ($P < 0.05$) significantly and independently associated with WBGD. In the longitudinal study, made with subjects at the highest tertiles of plasma TNF-alpha concentration ($n = 50$), plasma TNF-alpha concentration predicted a decline in WBGD independent of age, sex, BF, WHR [relative risk (RR) = 2.0; 95% confidence intervals (CI) = 1.2-2.4]. After further adjustment for plasma fasting FFA concentration, the predictive role of fasting plasma TNF-alpha concentration on WBGD (RR = 1.2; CI = 0.8-1.5) was no more significant. In conclusion, our study demonstrates that plasma TNF-alpha concentration is significantly associated with advancing age and that it predicts the impairment in insulin action with advancing age.

L4 ANSWER 44 OF 159 MEDLINE DUPLICATE 33

ACCESSION NUMBER: 1998291384 MEDLINE
DOCUMENT NUMBER: 98291384 PubMed ID: 9627914
TITLE: Zinc may regulate serum **leptin** concentrations in humans.
AUTHOR: Mantzoros C S; Prasad A S; Beck F W; Grabowski S; Kaplan J; Adair C; Brewer G J
CORPORATE SOURCE: Department of Internal Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.
CONTRACT NUMBER: DK R37 28082 (NIDDK)
DK28082 (NIDDK)
DK31401 (NIDDK)
SOURCE: JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION, **(1998 Jun)** 17 (3) 270-5.
Journal code: H51; 8215879. ISSN: 0731-5724.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980910
Last Updated on STN: 20000303
Entered Medline: 19980828

AB OBJECTIVE: **Leptin**, the product of the ob gene, plays a key role in a feedback loop that maintains energy balance by signaling the state of energy stores to the brain and by influencing the regulation of appetite and energy metabolism. Zinc also plays an important role in appetite regulation. Thus, we evaluated the relationship between zinc status and the **leptin** system in humans. METHODS: We studied nine healthy men with marginal zinc deficiency, induced by dietary means, before and after zinc supplementation. RESULTS: Zinc restriction decreased **leptin** levels while zinc supplementation of zinc-depleted subjects increased circulating **leptin** levels. In addition, zinc supplementation increased IL-2 and TNF-alpha production that could be responsible for the observed increase in **leptin** concentrations. CONCLUSIONS: Zinc may influence serum **leptin** levels, possibly by increasing the production of IL-2 and TNF-alpha.

L4 ANSWER 45 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:199888 BIOSIS
DOCUMENT NUMBER: PREV199800199888
TITLE: Inhibition of cholecystokinin (CCK)-stimulated amylase release by **leptin** in rat pancreatic **tumor** cells.
AUTHOR(S): Harris, D. M. (1); Flannigan, K. I. (1); Go, V. L. W. (1); Wu, S. V.
CORPORATE SOURCE: (1) Cent. Hum. Nutr., UCLA Sch. Med., Los Angeles, CA 90095
USA
SOURCE: FASEB Journal, (**March 17, 1998**) Vol. 12, No. 4, pp. A260.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology 98, Part 1 San Francisco, California, USA April 18-22, 1998 Federation of American Societies for Experimental Biology
. ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 46 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:333402 BIOSIS
DOCUMENT NUMBER: PREV199800333402
TITLE: Effect of exercise during pregnancy on two metabolic markers: **Tumor** necrosis factor-alpha (TNF-alpha) and **leptin** (L.
AUTHOR(S): Clapp, J. F. (1); Blum, W. F.; Kiess, W.
CORPORATE SOURCE: (1) MetroHealth Med. Center, Cleveland, OH USA
SOURCE: Medicine and Science in Sports and Exercise, (**May, 1998**) Vol. 30, No. 5 SUPPL., pp. S259.
Meeting Info.: 45th Annual Meeting of the American College of Sports Medicine Orlando, Florida, USA June 3-6, 1998
American College of Sports Medicine
. ISSN: 0195-9131.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 47 OF 159 MEDLINE DUPLICATE 34
ACCESSION NUMBER: 1998200234 MEDLINE
DOCUMENT NUMBER: 98200234 PubMed ID: 9541164
TITLE: Pioglitazone time-dependently reduces **tumour** necrosis factor-alpha level in muscle and improves metabolic abnormalities in Wistar fatty rats.
AUTHOR: Murase K; Odaka H; Suzuki M; Tayuki N; Ikeda H
CORPORATE SOURCE: Pharmaceutical Research Laboratories I, Takeda Chemical Industries, Osaka, Japan.
SOURCE: DIABETOLOGIA, **(1998 Mar)** 41 (3) 257-64.
Journal code: E93; 0006777. ISSN: 0012-186X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980609
Last Updated on STN: 19980609
Entered Medline: 19980526

AB In order to evaluate the relationship between **tumour** necrosis factor-alpha (TNF-alpha) level in muscle and metabolic abnormalities in obesity and diabetes mellitus, pioglitazone, a novel insulin-sensitizing agent, was administered to Wistar fatty rats and time-dependent changes in muscle TNF-alpha content and plasma indicators of diabetes and obesity were measured. Wistar fatty rats were hyperglycaemic, hyperlipidaemic and hyperinsulinaemic, and their plasma and muscle TNF-alpha levels were two or more times higher than those in normal lean rats at 16 weeks of age. When pioglitazone was administered to fatty rats at a dose of 3 mg kg(-1) day(-1), the plasma triglyceride level and TNF-alpha levels in plasma and muscle decreased time-dependently, and reached the levels of lean rats within 4 days. Plasma glucose and insulin levels also decreased time-dependently with pioglitazone, but on day 4, these levels were still much higher than the levels in lean rats. Neutral sphingomyelinase (SMase) activity in muscle of fatty rats was two times higher than that in lean rats and was lowered to the level of that in lean rats by 4 days' pioglitazone administration. The plasma **leptin** level in fatty rats was 8 times higher than that in lean rats, but pioglitazone did not affect the level during the 4-day administration period. These results suggest that an increase in TNF-alpha production and subsequent activation of SMase in muscle leads to metabolic abnormalities in obesity and diabetes and that antidiabetic activity of pioglitazone is deeply associated with the suppression of TNF-alpha production.

L4 ANSWER 48 OF 159 MEDLINE DUPLICATE 35

ACCESSION NUMBER: 1998394625 MEDLINE
DOCUMENT NUMBER: 98394625 PubMed ID: 9727642
TITLE: Chronic ethanol consumption induces the production of **tumor** necrosis factor-alpha and related cytokines in liver and adipose tissue.
AUTHOR: Lin H Z; Yang S Q; Zeldin G; Diehl A M
CORPORATE SOURCE: Department of Medicine, Johns Hopkins University, Baltimore, Maryland 21205, USA.
SOURCE: ALCOHOLISM, CLINICAL AND EXPERIMENTAL RESEARCH, **(1998 Aug)** 22 (5 Suppl) 231S-237S.
Journal code: 35X; 7707242. ISSN: 0145-6008.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981216

AB Increases in monocyte/macrophage production of the proinflammatory cytokine, **tumor** necrosis factor-alpha (TNF-alpha), parallel the evolution of liver injury in rats and humans with alcoholic liver disease. However, the possibility that TNF-alpha expression may be induced in other cell populations before serious liver disease develops has not been evaluated. To clarify this issue, mRNAs and/or protein levels of TNF-alpha and cytokines [interleukin (IL)-6, IL-10, transforming growth factor-beta (TGF)-beta, IL-12, and interferon-gamma] that regulate its biological

activity were measured in sera, liver, and adipose tissues of rats that had developed hepatic steatosis after consuming ethanol-containing diets for 6 weeks. Cytokine expression in the ethanol-fed groups was compared with that of pair-fed controls rats that had received isocaloric amounts of a similar, ethanol-free diet for the same time period. Animals were studied both before and after a surgical stress (partial hepatectomy) that is known to provoke cytokine production. Chronic ethanol consumption led to increased serum concentrations of TNF and related cytokines, at least in part, by inducing the overproduction of these factors in the liver and peripheral adipose tissues. Despite the pair-feeding protocol that ensured similar calorie consumption in both groups, adipose tissues in ethanol-fed rats also expressed more **leptin**, a TNF-alpha-inducible mRNA that encodes an appetite-suppressing hormone. Thus, white adipose tissue can be an important source of cytokines in nonobese animals and may be a target for ethanol's actions. These data implicate TNF-alpha as a potential mediator of the nutritional-metabolic aberrations that often accompany chronic alcohol intake, even in the absence of advanced liver disease.

L4 ANSWER 49 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:18300 BIOSIS
DOCUMENT NUMBER: PREV199900018300
TITLE: Dopamine regulates Na,K-ATPase by a MAPK-dependent Ras-independent mechanism.
AUTHOR(S): Guerrero, C.; Lecuona, E.; Pesce, L.; Ridge, K. M.; Sznajder, J. I.
CORPORATE SOURCE: Pulmonary Critical Care Med., Michael Reese Hosp., Univ. Ill. at Chicago, Chicago, IL 60616 USA
SOURCE: Molecular Biology of the Cell, (**Nov.**, **1998**) Vol. 9, No. SUPPL., pp. 229A.
Meeting Info.: 38th Annual Meeting of the American Society for Cell Biology San Francisco, California, USA December 12-16, 1998 American Society for Cell Biology
. ISSN: 1059-1524.
DOCUMENT TYPE: Conference
LANGUAGE: English

DUPLICATE 36

L4 ANSWER 50 OF 159 MEDLINE
ACCESSION NUMBER: 1998293274 MEDLINE
DOCUMENT NUMBER: 98293274 PubMed ID: 9629629
TITLE: Obesity in female life--from molecular to clinical aspects.
AUTHOR: Geisthovel F
SOURCE: ZENTRALBLATT FUR GYNAKOLOGIE, **(1998)** 120 (5) 223-34. Ref: 91
Journal code: Y5S; 21820100R. ISSN: 0044-4197.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980820
Last Updated on STN: 20000303

Entered Medline: 19980810

AB Obesity gains increasing prevalence world-wide. Multifactorially caused it presents itself in numerous heterogeneous phenotypes with a wide spectrum of clinical symptoms. The full-blown female obesity syndrome is initiated already in childhood, associated with ovarian hyperandrogenaemia (polycystic ovary syndrome) in the reproductive phase, and characterised by increasing co-morbidity (**cancer**; metabolic syndrome; arteriosclerosis) in the postmenopausal state leading to shortened longevity. Due to the complexity of psychic, somatic and endocrine-metabolic disturbances a causal break-through in the treatment of the disease could not be achieved yet, but the enhanced basal understanding and recently investigated pharmaceutical principles might enable to improve the therapeutical approaches.

L4 ANSWER 51 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:425119 BIOSIS
DOCUMENT NUMBER: PREV199800425119
TITLE: Plasma **leptin** and **tumor** necrosis factor alpha in type I diabetes mellitus.
AUTHOR(S): Lechleitner, M.; Koch, T.; Sturm, W.; Gotsch, C.; Hoppichler, H.; Patsch, J. R.
CORPORATE SOURCE: Intern. Med., Univ. Innsbruck, Innsbruck Austria
SOURCE: Diabetologia, (**Aug.**, **1998**) Vol. 41, No. SUPPL. 1, pp. A219.
Meeting Info.: 34th Annual Meeting of the European Association for the Study of Diabetes Barcelona, Spain September 11, 1998 European Association for the Study of Diabetes
. ISSN: 0012-186X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 52 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:425109 BIOSIS
DOCUMENT NUMBER: PREV199800425109
TITLE: Effects of storage, anticoagulants and freeze-thaw cycles on stability of IL-6, TNF-alpha and **leptin**.
AUTHOR(S): Flower, C. L.; Ahuja, R. H.; Yudkin, J. S.; Coppack, S. W.; Mohammed-Ali, V.
CORPORATE SOURCE: UCLMS, London UK
SOURCE: Diabetologia, (**Aug.**, **1998**) Vol. 41, No. SUPPL. 1, pp. A217.
Meeting Info.: 34th Annual Meeting of the European Association for the Study of Diabetes Barcelona, Spain September 11, 1998 European Association for the Study of Diabetes
. ISSN: 0012-186X.
DOCUMENT TYPE: Conference
LANGUAGE: English

DUPLICATE 37

L4 ANSWER 53 OF 159 MEDLINE
ACCESSION NUMBER: 1998120540 MEDLINE
DOCUMENT NUMBER: 98120540 PubMed ID: 9458919
TITLE: IL-1 beta mediates **leptin** induction during inflammation.
AUTHOR: Faggioni R; Fantuzzi G; Fuller J; Dinarello C A; Feingold K

R; Grunfeld C

CORPORATE SOURCE: Metabolism Section, Veterans Affairs Medical Center, University of California, San Francisco 94121, USA.

CONTRACT NUMBER: AI-15614 (NIAID)
DK-40990 (NIDDK)
DK-49448 (NIDDK)

SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, **(1998 Jan)** 274 (1 Pt 2) R204-8.
Journal code: 3U8; 0370511. ISSN: 0002-9513.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980306
Last Updated on STN: 20000303
Entered Medline: 19980223

AB Interleukins (IL) are key mediators of the host response to infection and inflammation. **Leptin** is secreted by adipose tissue and plays an important role in the control of food intake. Administration of lipopolysaccharide (LPS), **tumor** necrosis factor (TNF), or IL-1 acutely increases **leptin** mRNA and protein levels. To investigate the role of IL-1 beta and IL-6 in **leptin** expression during inflammation, we used IL-1 beta-deficient (-/-) and IL-6 -/- mice. Mice were injected intraperitoneally with LPS or subcutaneously with turpentine, as models of systemic or local inflammation, respectively. In IL-1 beta +/+ mice, both LPS and turpentine increased **leptin** mRNA and circulating **leptin**. In contrast, neither LPS nor turpentine increased **leptin** levels in IL-1 beta -/- mice. In IL-6 +/+ or IL-6 -/- mice, turpentine increased **leptin** protein to comparable levels. We conclude that IL-1 beta is essential for **leptin** induction by both LPS and turpentine in mice, but IL-6 is not.

L4 ANSWER 54 OF 159 MEDLINE DUPLICATE 38

ACCESSION NUMBER: 1998400137 MEDLINE
DOCUMENT NUMBER: 98400137 PubMed ID: 9730686

TITLE: Hypothalamic control of FSH and LH by FSH-RF, LHRH, cytokines, **leptin** and nitric oxide.

AUTHOR: McCann S M; Kimura M; Walczewska A; Karanth S; Rettori V; Yu W H

CORPORATE SOURCE: Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, La., USA.

CONTRACT NUMBER: DK4390 (NIDDK)
MH51853 (NIMH)

SOURCE: NEUROIMMUNOMODULATION, **(1998 May-Aug)** 5 (3-4) 193-202. Ref: 55
Journal code: CCL; 9422763. ISSN: 1021-7401.

PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 20000303
Entered Medline: 19981103

AB Gonadotropin secretion by the pituitary gland is under the control of luteinizing hormone-releasing hormone (LHRH) and the putative follicle-stimulating hormone-releasing factor (FSHRF). Lamprey III LHRH is a potent FSHRF in the rat and appears to be resident in the FSH controlling area of the rat hypothalamus. It is an analog of mammalian LHRH and may be the long-sought FSHRF. Gonadal steroids feedback at hypothalamic and pituitary levels to either inhibit or stimulate the release of LH and FSH, which is also affected by inhibin and activin secreted by the gonads. Important control is exercised by acetylcholine, norepinephrine (NE), dopamine, serotonin, melatonin and glutamic acid (GA). Furthermore, LH and FSH also act at the hypothalamic level to alter secretion of gonadotropins. More recently, growth factors have been shown to have an important role. Many peptides act to inhibit or increase release of LH, and the sign of their action is often reversed by estrogen.

A number of cytokines act at the hypothalamic level to suppress acutely the release of LH but not FSH. NE, GA and oxytocin stimulate LHRH release by activation of neural nitric oxide synthase (nNOS). The pathway is as follows: oxytocin and/or GA activate NE neurons in the medial basal hypothalamus (MBH) that activate NOergic neurons by alpha1 receptors. The NO released diffuses into LHRH terminals and induces LHRH release by activation of guanylate cyclase (GC) and cyclooxygenase. NO not only controls release of LHRH bound for the pituitary, but also that which induces mating by actions in the brain stem. An exciting recent development has been the discovery of the adipocyte hormone, **leptin**, a cytokine related to **tumor** necrosis factor-alpha (TNF-alpha). In the male rat, **leptin** exhibits a high potency to stimulate FSH and LH release from hemipituitaries incubated in vitro, and increases the release of LHRH from MBH explants by stimulating the release of NO. LHRH and **leptin** release LH by activation of NOS in the gonadotropes. The NO released activates GC that releases cyclic GMP which induces LH release. **Leptin** induces LH release in conscious, ovariectomized estrogen-primed female rats, presumably by stimulating LHRH release. At the effective dose of estrogen to activate LH release, FSH release is inhibited. **Leptin** may play an important role in induction of puberty and control of LHRH release in the adult as well.

L4 ANSWER 55 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1998:534100 BIOSIS

DOCUMENT NUMBER: PREV199800534100

TITLE: Effects of a 3 week hypocaloric diet on PPARgamma UCP2, TNFalpha and **leptin** mRNA levels in non diabetic obese women.

AUTHOR(S): Bastard, J. P. (1); Hainque, B. (1); Dusserre, E.; Bruckert, E.; Vallier, P.; Robin, D.; Jardel, C. (1); Forest, C.; Vidal, H.

CORPORATE SOURCE: (1) Serv. Biochemie B: Hopital de la Salpetriere, Paris France

SOURCE: International Journal of Obesity, (**Aug.**, **1998**) Vol. 22, No. SUPPL. 3, pp. S172. Meeting Info.: Eighth International Congress on Obesity Paris, France August 29-September 3, 1998 International Association for the Study of Obesity . ISSN: 0307-0565.

DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 56 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:522926 BIOSIS
DOCUMENT NUMBER: PREV199800522926
TITLE: Plasma **leptin**, **tumour** necrosis factor-alpha and the sympathetic nervous system in the cachexia associated with chronic heart failure.
AUTHOR(S): Murdoch, D. R.; Rooney, E.; Dargie, H. J.; Shapiro, D.; Morton, J. J.; McMurray, J. J. V.
CORPORATE SOURCE: MRC Clin. Res. Initiative Heart Failure, Univ. Glasgow, Glasgow UK
SOURCE: European Heart Journal, (**Aug.**, **1998**) Vol. 19, No. ABST. SUPPL., pp. 170.
Meeting Info.: XXth Congress of the European Society of Cardiology Vienna, Austria August 22-26, 1998 European Society of Cardiology
. ISSN: 0195-668X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 57 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:534088 BIOSIS
DOCUMENT NUMBER: PREV199800534088
TITLE: **Leptin** receptor (OB-Rb) in human lung tissue and lung **cancer** cell lines.
AUTHOR(S): Tsuchiya, T.; Shimizu, H.; Ohtani, K.; Sato, N.; Mori, M.
CORPORATE SOURCE: First Dep. Internal Med., Gunma Univ. Sch. Med., Maebashi Japan
SOURCE: International Journal of Obesity, (**Aug.**, **1998**) Vol. 22, No. SUPPL. 3, pp. S169.
Meeting Info.: Eighth International Congress on Obesity Paris, France August 29-September 3, 1998 International Association for the Study of Obesity
. ISSN: 0307-0565.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 58 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:291384 BIOSIS
DOCUMENT NUMBER: PREV199800291384
TITLE: **Leptin**, weight loss and the inflammatory response in gastrointestinal **cancer**.
AUTHOR(S): Wallace, A. M. (1); Sattar, N. (1); McMillan, D. C.
CORPORATE SOURCE: (1) Univ. Dep. Clinical Biochem., Royal Infirmary, Glasgow G4 0SF UK
SOURCE: Journal of Endocrinology, (**March**, **1998**) Vol. 156, No. SUPPL., pp. P138.
Meeting Info.: 17th Joint Meeting of the British Endocrine Societies Edinburgh, Scotland, UK March 23-25, 1998
British Endocrine Societies
. ISSN: 0022-0795.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 59 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1998:532450 BIOSIS
DOCUMENT NUMBER: PREV199800532450
TITLE: Cytokines and **leptin**: Regulation in growth and disease.
AUTHOR(S): Houseknecht, K. L. (1)
CORPORATE SOURCE: (1) Purdue Univ., West Lafayette, IN USA
SOURCE: Journal of Dairy Science, (1998) Vol. 81, No. SUPPL. 1, pp. 120.
Meeting Info.: Joint Meeting of the American Dairy Science Association and the American Society of Animal Science Denver, Colorado, USA July 28-31, 1998 Amercian Society of Animal Science
. ISSN: 0022-0302.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 60 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:532453 BIOSIS
DOCUMENT NUMBER: PREV199800532453
TITLE: Physiological roles of **leptin**, myostatin, and other cytokines.
AUTHOR(S): Spurlock, M. E. (1)
CORPORATE SOURCE: (1) Purina Mills Inc., St. Louis, MO USA
SOURCE: Journal of Dairy Science, (1998) Vol. 81, No. SUPPL. 1, pp. 120.
Meeting Info.: Joint Meeting of the American Dairy Science Association and the American Society of Animal Science Denver, Colorado, USA July 28-31, 1998 Amercian Society of Animal Science
. ISSN: 0022-0302.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 61 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:533851 BIOSIS
DOCUMENT NUMBER: PREV199800533851
TITLE: **Leptin** and TNFalpha effects on human adipose tissue.
AUTHOR(S): Zhang, H. H.; Kumar, S.; Barnett, A.; Eggo, M. C.
CORPORATE SOURCE: Dep. Med., Univ. Birmingham, Queen Elizabeth Hosp., Birmingham B15 2TH UK
SOURCE: International Journal of Obesity, (**Aug.**, **1998**) Vol. 22, No. SUPPL. 3, pp. S104.
Meeting Info.: Eighth International Congress on Obesity Paris, France August 29-September 3, 1998 International Association for the Study of Obesity
. ISSN: 0307-0565.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 62 OF 159 MEDLINE DUPLICATE 39
ACCESSION NUMBER: 1998121221 MEDLINE
DOCUMENT NUMBER: 98121221 PubMed ID: 9461323
TITLE: Hyperphagia in children with craniopharyngioma is associated with hyperleptinaemia and a failure in the downregulation of appetite.

AUTHOR: Roth C; Wilken B; Hanefeld F; Schroter W; Leonhardt U
CORPORATE SOURCE: Department of Paediatrics, University of Gottingen, Germany.
SOURCE: EUROPEAN JOURNAL OF ENDOCRINOLOGY, **(1998 Jan)** 138 (1) 89-91.
Journal code: BXU; 9423848. ISSN: 0804-4643.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980312
Last Updated on STN: 20000303
Entered Medline: 19980304

AB Patients with craniopharyngioma frequently suffer from severe obesity. **Leptin** induces an inhibition of appetite via hypothalamic receptors. This study was undertaken to investigate whether a relationship exists between serum **leptin** levels and pituitary/hypothalamic lesions in craniopharyngioma patients. Serum **leptin** levels were evaluated by RIA in 14 patients (age 7-21 years; 7 females, 7 males) after they had undergone neurosurgical treatment for craniopharyngioma. Normal controls had a positive correlation between **leptin** levels and body mass index (BMI) with higher levels in the females than in the males. Significantly elevated **leptin** levels with respect to BMI were found in 11 craniopharyngioma patients who had been affected by a suprasellar **tumour**, whereas 3 patients with an intrasellar **tumour** had lower, almost normal serum **leptin** levels. Our data suggest that craniopharyngioma patients develop hypothalamic obesity because their hypothalamic structures are insensitive to endogenous **leptin**. The elevated serum **leptin** concentrations found only in patients with a suprasellar **tumour** may be explained by a disturbed feedback mechanism from the hypothalamic **leptin** receptors to the adipose tissue.

L4 ANSWER 63 OF 159 MEDLINE DUPLICATE 40
ACCESSION NUMBER: 1999092383 MEDLINE
DOCUMENT NUMBER: 99092383 PubMed ID: 9875224
TITLE: Differential regulation of mouse uncoupling proteins among brown adipose tissue, white adipose tissue, and skeletal muscle in chronic beta 3 adrenergic receptor agonist treatment.
AUTHOR: Yoshitomi H; Yamazaki K; Abe S; Tanaka I
CORPORATE SOURCE: Tsukuba Research Laboratories, Eisai Co., Ltd., Ibaraki, Japan.. h1-yoshitomi@eisai.co.jp
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1998 Dec 9)** 253 (1) 85-91.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990128
Last Updated on STN: 20000303
Entered Medline: 19990113

AB Uncoupling proteins (UCPs) are inner mitochondrial membrane transporters that dissipate the proton gradient, releasing stored energy as heat, without coupling to other energy-consuming processes. Therefore, the UCPs are thought to be important determinants of the metabolic efficiency. To elucidate relationships between the UCPs expressions and insulin sensitivity improvement, we treated KK-Ay mice with beta 3 adrenergic receptor agonist for 21 days and examined the changes of the UCPs mRNA expressions in various tissues. Chronic treatment of a specific beta 3 adrenergic receptor agonist, CL316,243 (0.2 mg/kg body weight/day s.c.) markedly increased the expressions of uncoupling protein 1 (UCP1), uncoupling protein 2 (UCP2), and uncoupling protein 3 (UCP3) by 14-fold, 6-fold, and 16-fold, respectively, in the brown adipose tissue (BAT). The UCP1 and UCP3 mRNA expressions in the white adipose tissue (WAT) were also increased by 12-fold and 9-fold, respectively, but the UCP2 mRNA expression was not changed in this tissue. Interestingly, the UCP2 and UCP3 mRNA expressions were strikingly decreased in the skeletal muscle and heart. Particularly, the UCP3 mRNA expression level in the skeletal muscle was dropped to 10% of that of the saline-treated control mice, indicating that the UCPs mRNA expressions are regulated in tissue-specific ways. The concentrations of plasma insulin and circulating free fatty acid (FFA) were significantly decreased, suggesting that they correlate with the reductions of the UCP2 and UCP3 mRNA expressions in the skeletal muscle and heart. It has been thought that the UCP1 and UCP3 mRNA expressions in the BAT and WAT are mainly controlled by the hypothalamus via the sympathetic nervous system, while the levels of insulin, FFA or both may play important roles in the control of the UCP2 and UCP3 mRNA expressions in the skeletal muscle an heart.

L4 ANSWER 64 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:533770 BIOSIS
DOCUMENT NUMBER: PREV199800533770
TITLE: A novel role for **tumor** necrosis factor receptor 1 as regulator of **leptin** secretion.
AUTHOR(S): Sethi, J. K.; Uysal, K. T.; Wiesbrock, S. M.; Hotamisligil, G. S.
CORPORATE SOURCE: Dep. Nutrtion, Harvard Sch. Public Health, Boston, MA USA
SOURCE: International Journal of Obesity, (**Aug.**, **1998**) Vol. 22, No. SUPPL. 3, pp. S80. Meeting Info.: Eighth International Congress on Obesity Paris, France August 29-September 3, 1998 International Association for the Study of Obesity . ISSN: 0307-0565.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 65 OF 159 MEDLINE DUPLICATE 41
ACCESSION NUMBER: 1998288166 MEDLINE
DOCUMENT NUMBER: 98288166 PubMed ID: 9622598
TITLE: Lipopolysaccharide (LPS)- and muramyl dipeptide (MDP)-induced anorexia during refeeding following acute fasting: characterization of brain cytokine and neuropeptide systems mRNAs.
AUTHOR: Gayle D; Ilyin S E; Flynn M C; Plata-Salaman C R
CORPORATE SOURCE: Division of Molecular Biology, School of Life and Health

Sciences, University of Delaware, Newark, DE 19716-2590, USA.

SOURCE: BRAIN RESEARCH, **(1998 Jun 8)** 795 (1-2) 77-86.
Journal code: B5L; 0045503. ISSN: 0006-8993.

PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980828
Last Updated on STN: 19980828
Entered Medline: 19980819

AB We investigated the effectiveness of lipopolysaccharide (LPS) and muramyl dipeptide (MDP) administered into the brain to induce anorexia in acutely fasted Wistar rats allowed to refeed. We also assayed for changes in mRNA levels of IL-1 system components, TNF-alpha, TGF-beta1, glycoprotein 130 (gp 130), **leptin** receptor (OB-R), pro-opiomelanocortin (POMC), neuropeptide Y (NPY), glucocorticoid receptor (GR), and CRF receptor (CRF-R) in selected brain regions. The data show that LPS and MDP induced anorexia differentially during refeeding. LPS-induced anorexia was of a stronger magnitude and duration than that of MDP. RNase protection assays showed that LPS and MDP significantly increased the expression of IL-1beta, IL-1 receptor type I, and TNF-alpha mRNAs in the cerebellum, hippocampus, and hypothalamus; LPS was more potent in all cases. MDP treatment, on the other hand, induced a stronger increase in hypothalamic levels of IL-1 receptor antagonist (IL-1Ra) and TGF-beta1 mRNAs relative to LPS. In addition, competitive RT-PCR analysis showed that LPS induced an eleven-fold increase in IL-1alpha mRNA in the hypothalamus relative to vehicle. These findings suggest that LPS and MDP mediate anorexia through different cytokine mechanisms. A stronger up-regulation of anti-inflammatory cytokines (IL-1Ra and TGF-beta1) mRNA expression by MDP may be involved in the weaker MDP-induced anorexia relative to LPS. No significant changes were observed in the peptide components examined except for an up-regulation in cerebellar gp 130 mRNA and down-regulation of hypothalamic GR mRNA expression in response to LPS or MDP. This study shows that LPS and MDP induce anorexia in fasted rats allowed to refeed, and suggests an important role for endogenous cytokine-cytokine interactions.

L4 ANSWER 66 OF 159 MEDLINE DUPLICATE 42
ACCESSION NUMBER: 1998317521 MEDLINE
DOCUMENT NUMBER: 98317521 PubMed ID: 9644096
TITLE: Importance of TNF-alpha and **leptin** in obesity and insulin resistance: a hypothesis on the impact of physical exercise.

AUTHOR: Halle M; Berg A; Northoff H; Keul J
CORPORATE SOURCE: Dept. of Rehabilitation, Prevention, and Sports Medicine, Freiburg University Hospital, Germany.

SOURCE: EXERCISE IMMUNOLOGY REVIEW, **(1998)** 4 77-94. Ref: 114
Journal code: CR2; 9505535. ISSN: 1077-5552.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)

LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19981006
Last Updated on STN: 20000303
Entered Medline: 19980924

AB Obesity is associated with an increased incidence of insulin resistance, dyslipoproteinemia, and hypercoagulability. In a more recently established hypothesis of body weight control and regulation of metabolism, the adipocyte secretes **leptin** and locally expresses TNF-alpha, the latter being responsible for the expression of metabolic cardiovascular risk factors. TNF-a mRNA expression and TNF-alpha protein are greatly increased in adipose tissue from obese animals and humans. Elevated TNF-alpha expression induces insulin resistance by downregulating the tyrosine kinase activity of the insulin receptor and decreasing the expression of GLUT-4 glucose transporters. TNF-alpha also reduces lipoprotein lipase activity in white adipocytes, stimulates hepatic lipolysis, and increases plasminogen activator inhibitor-1 content in adipocytes. Moreover, adipocytes secrete **leptin**, a molecule with a secondary cytokine structure whose concentrations correlate with the amount of fat tissue. Increased **leptin** levels downregulate appetite and increase sympathetic activity and thermogenesis in the hypothalamus. Diet-induced weight loss reduces adipose TNF-alpha expression and serum **leptin** levels and is associated with improved insulin sensitivity and lipid metabolism. Although exercise has also been shown to reduce **leptin** levels, an influence on TNF-a expression in adipocytes or muscle cells has not yet been demonstrated.

L4 ANSWER 67 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:364488 BIOSIS
DOCUMENT NUMBER: PREV199800364488
TITLE: PPARgamma activators improve glucose homeostasis by stimulating fatty acid uptake in the adipocytes.
AUTHOR(S): Martin, Genevieve; Schoonjans, Kristina; Staels, Bart; Auwerx, Johan (1)
CORPORATE SOURCE: (1) U.325 INSERM, Dep. Atherosclerose, Inst. Pasteur de Lille, 1 Rue Calmette, 59019 Lille Cedex France
SOURCE: Atherosclerosis, (**April**, **1998**) Vol. 137, No. SUPPL., pp. S75-S80.
ISSN: 0021-9150.
DOCUMENT TYPE: General Review
LANGUAGE: English

AB It is currently thought that the effects of PPARgamma activation on glucose homeostasis may be due to the effect of this nuclear receptor on the production of adipocyte-derived signalling molecules, which affect muscle glucose metabolism. Potential signalling molecules derived from adipocytes and modified by PPARgamma activation include TNFalpha and **leptin**, which both interfere with glucose homeostasis. In addition to its effects on these proteins, PPARgamma also profoundly affects fatty acid metabolism. Activation of PPARgamma will selectively induce the expression of several genes involved in fatty acid uptake, such as lipoprotein lipase, fatty acid transport protein and acyl-CoA synthetase, in adipose tissue without changing their expression in muscle tissue. This co-ordinate regulation of fatty acid partitioning by PPARgamma results in an adipocyte 'FFA steal' causing a relative depletion of fatty acids in the muscle. Based on the well established interference of muscle fatty acid and glucose metabolism it is hypothesized that reversal of muscle fatty acid accumulation will contribute to the improvement in whole body

glucose homeostasis.

L4 ANSWER 68 OF 159 MEDLINE
ACCESSION NUMBER: 1998441839 MEDLINE
DOCUMENT NUMBER: 98441839 PubMed ID: 9769703
TITLE: Signaling via JAK tyrosine kinases: growth hormone receptor as a model system.
AUTHOR: Carter-Su C; Smit L S
CORPORATE SOURCE: Department of Physiology, University of Michigan Medical School, Ann Arbor 48109-0622, USA.
CONTRACT NUMBER: R01-DK34171 (NIDDK)
R01-DK48293 (NIDDK)
SOURCE: RECENT PROGRESS IN HORMONE RESEARCH, **(1998)** 53 61-82; discussion 82-3. Ref: 78
Journal code: R1D; 0404471. ISSN: 0079-9963.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981106

AB During the past 4 years, significant progress has been made in elucidating the earliest events following binding of ligands to members of the cytokine receptor superfamily. This is a rapidly growing family of receptors that currently includes receptors for growth hormone (GH); prolactin; erythropoeitin; granulocyte colony-stimulating factor; granulocyte macrophage colony-stimulating factor; interleukin(IL)s 2-7, 9-13, 15; interferon (IFN)-alpha, beta, and gamma; thrombopoietin; **leptin**; oncostatin M; **leukemia** inhibitory factor (LIF); ciliary neurotrophic factor; and cardiotropin-1. Despite their diverse physiological effects in the body, ligands that bind to members of this family share multiple signaling pathways. An early and most likely initiating event for all of them is the activation of one or more members of the Janus (or JAK) family of tyrosine kinases. The activated JAK kinases, which form a complex with the cytokine receptor subunits, phosphorylate themselves as well as the receptor. These phosphorylated tyrosines form binding sites for various signaling molecules that are themselves thought to be phosphorylated by JAK kinases, including 1) signal transducers and activators of transcription (Stats), which regulate transcription; 2) She proteins that recruit Grb2-SOS complexes, thereby initiating the Ras-MAP kinase pathway; and 3) insulin receptor substrate (IRS) proteins that are thought to regulate metabolic events in the cell. Additional other signaling molecules have been implicated in signaling by some cytokines, including protein kinase C, SH2-B beta, and intracellular Ca. This review uses the GH receptor as a model system for studying cytokine signaling and summarizes some of the data used to establish JAK2 as a GH receptor-associated tyrosine kinase and to identify signaling molecules that lie downstream of JAK2. Since these pathways are shared by multiple cytokines, this review also discusses factors that might contribute to specificity of response to different cytokines.

L4 ANSWER 69 OF 159 MEDLINE DUPLICATE 43
ACCESSION NUMBER: 1998099248 MEDLINE
DOCUMENT NUMBER: 98099248 PubMed ID: 9438411
TITLE: **Leptin** regulates proinflammatory immune responses.
AUTHOR: Loffreda S; Yang S Q; Lin H Z; Karp C L; Brengman M L; Wang D J; Klein A S; Bulkley G B; Bao C; Noble P W; Lane M D; Diehl A M
CORPORATE SOURCE: Department of Medicine, Johns Hopkins University, Baltimore, Maryland 21205, USA.
SOURCE: FASEB JOURNAL, **(1998 Jan)** 12 (1) 57-65.
Journal code: FAS; 8804484. ISSN: 0892-6638.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980224
Last Updated on STN: 20000303
Entered Medline: 19980209

AB Obesity is associated with an increased incidence of infection, diabetes, and cardiovascular disease, which together account for most obesity-related morbidity and mortality. Decreased expression of **leptin** or of functional **leptin** receptors results in hyperphagia, decreased energy expenditure, and obesity. It is unclear, however, whether defective **leptin**-dependent signal transduction directly promotes any of the conditions that frequently complicate obesity. Abnormalities in **tumor** necrosis factor alpha expression have been noted in each of the above comorbid conditions, so **leptin** deficiency could promote these complications if **leptin** had immunoregulatory activity. Studies of rodents with genetic abnormalities in **leptin** or **leptin** receptors revealed obesity-related deficits in macrophage phagocytosis and the expression of proinflammatory cytokines both in vivo and in vitro. Exogenous **leptin** up-regulated both phagocytosis and the production of proinflammatory cytokines. These results identify an important and novel function for **leptin**: up-regulation of inflammatory immune responses, which may provide a common pathogenetic mechanism that contributes to several of the major complications of obesity.

L4 ANSWER 70 OF 159 MEDLINE DUPLICATE 44
ACCESSION NUMBER: 1998290760 MEDLINE
DOCUMENT NUMBER: 98290760 PubMed ID: 9625866
TITLE: Role of tyrosine phosphorylation in **leptin** activation of ATP-sensitive K+ channels in the rat insulinoma cell line CRI-G1.
AUTHOR: Harvey J; Ashford M L
CORPORATE SOURCE: Department of Biomedical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK.
SOURCE: JOURNAL OF PHYSIOLOGY, **(1998 Jul 1)** 510 (Pt 1) 47-61.
Journal code: JQV; 0266262. ISSN: 0022-3751.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980910
Last Updated on STN: 20000303
Entered Medline: 19980901

AB 1. Using whole-cell and cell-attached recording configurations, the role of phosphorylation in **leptin** activation of ATP-sensitive K+ (KATP) channels was examined in the rat CRI-G1 insulinoma cell line. 2. Whole-cell current clamp recordings demonstrated that, following dialysis with the non-hydrolysable ATP analogue 5'-adenylylimidodiphosphate (AMP-PNP; 3-5 mM), the **leptin**-induced hyperpolarization and increase in K+ conductance were completely inhibited. 3. Under current clamp conditions, application of the broad-spectrum protein kinase inhibitor H-7 (10 microM) had no effect on the resting membrane potential or slope conductance of CRI-G1 insulinoma cells and did not occlude the actions of **leptin**. 4. Application of the tyrosine kinase inhibitors genistein (10 microM), tyrphostin B42 (10 microM) and herbimycin A (500 nM) all resulted in activation of KATP channels. In cell-attached recordings, the presence of tyrphostin B42 (10 microM) in the pipette solution activated tolbutamide-sensitive KATP channels in CRI-G1 cells. In contrast, the inactive analogues of genistein and tyrphostin B42 were without effect. 5. The serine/threonine-specific protein phosphatase inhibitors okadaic acid (50 nM) and cyclosporin A (1 microM) did not prevent or reverse **leptin** activation of KATP channels. In contrast, whole-cell dialysis with the tyrosine phosphatase inhibitor orthovanadate (500 microM) prevented the actions of both **leptin** and tyrphostin B42. 6. In conclusion, **leptin** activation of KATP channels appears to require inhibition of tyrosine kinases and subsequent dephosphorylation. This process is likely to occur prior to activation of phosphoinositide 3-kinase (PI 3-kinase) as wortmannin prevented activation of KATP channels by tyrphostin B42.

L4 ANSWER 71 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:533595 BIOSIS
DOCUMENT NUMBER: PREV199800533595
TITLE: Inhibition of OB gene expression and **leptin** production by chronic TNFalpha treatment of 3T3-F442A adipocytes.
AUTHOR(S): Tadayyon, M.; Haynes, A. C.; Holder, J. C.; Arch, J. R. S.
CORPORATE SOURCE: Dep. Vasc. Biol., Smithkline Beecham Pharm., Harlow UK
SOURCE: International Journal of Obesity, (**Aug.**, **1998**) Vol. 22, No. SUPPL. 3, pp. S32.
Meeting Info.: Eighth International Congress on Obesity Paris, France August 29-September 3, 1998 International Association for the Study of Obesity
. ISSN: 0307-0565.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 72 OF 159 MEDLINE DUPLICATE 45
ACCESSION NUMBER: 1998183393 MEDLINE
DOCUMENT NUMBER: 98183393 PubMed ID: 9514868
TITLE: Autocrine inhibition of **leptin** production by **tumor** necrosis factor-alpha (TNF-alpha) through TNF-alpha type-I receptor in vitro.
AUTHOR: Yamaguchi M; Murakami T; Tomimatsu T; Nishio Y; Mitsuda N; Kanzaki T; Kurachi H; Shima K; Aono T; Murata Y
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Osaka University

Medical School, Suita, Japan.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1998 Mar 6)** 244 (1) 30-4.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980416
Last Updated on STN: 20000303
Entered Medline: 19980409

AB The aim of this study was to find factors which regulate m-**leptin** secretion during pregnancy. Mouse parametrial adipocytes from day 13 of pregnancy were cultured with or without mouse placental lactogen (mPL)-I, mPL-II, or mouse **tumor** necrosis factor-alpha (mTNF-alpha) and mouse-**leptin** (m-**leptin**) concentration in the medium was assessed by RIA. Up to four days of mPL-I or mPL-II treatment did not affect m-**leptin** secretion. However, mTNF-alpha, which is produced by adipocytes, significantly inhibited m-**leptin** secretion in a dose- and time-dependent manner. Antibody to mTNF-alpha completely blocked the inhibitory effect of mTNF-alpha on m-**leptin** secretion. mTNF-alpha significantly inhibited the expression of m-**leptin** messenger RNA. Agonistic polyclonal antibody directed against the mTNF-type-I receptor (mTNF-RI) significantly inhibited m-**leptin** secretion, but the anti-mTNF-RII antibody did not change m-**leptin** secretion. Moreover, human TNF-alpha (h-TNF-alpha) also inhibited human-**leptin** (h-**leptin**) secretion by cultured human adipocytes collected from the subcutaneous fat of pregnant women. These results suggest that TNF-alpha, which is secreted by adipocytes, inhibits m-**leptin** secretion through mTNF-RI and suggest the presence of an autocrine or paracrine regulation of **leptin** secretion in human and mouse adipose tissue in vivo.

DUPLICATE 46

L4 ANSWER 73 OF 159 MEDLINE
ACCESSION NUMBER: 1998398377 MEDLINE
DOCUMENT NUMBER: 98398377 PubMed ID: 9729252
TITLE: Reciprocal changes in hypothalamic receptor binding and circulating **leptin** in anorectic **tumor** -bearing rats.
AUTHOR: Chance W T; Sheriff S; Moore J; Peng F; Balasubramaniam A
CORPORATE SOURCE: Medical Research Service, Veterans Affairs Medical Center, 3200 Vine Street, Cincinnati, OH 45220, USA.
CONTRACT NUMBER: GM 47122 (NIGMS)
SOURCE: BRAIN RESEARCH, **(1998 Aug 24)** 803 (1-2) 27-33.
Journal code: B5L; 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990607
Last Updated on STN: 20000303
Entered Medline: 19990526

AB Although reduced biological activity of the obese gene product, **leptin**, has been associated with obesity, little information is available concerning **leptin** alterations during anorexia. Therefore, we measured circulating **leptin** concentrations and

hypothalamic **leptin** binding in anorectic **tumor**-bearing and pair-fed control rats. Plasma concentrations of **leptin** decreased in **tumor**-bearing rats early in the course of **tumor** growth, and fell to nearly non-detectable levels during severe anorexia. The pair-fed control rats that ate the same amount of food as did the anorectic **tumor**-bearing rats exhibited a 50% decrease in plasma **leptin** concentration. Concentrations of free fatty acids were elevated in both **tumor**-bearing and pair-fed groups, while circulating levels of triglycerides were increased only in anorectic **tumor**-bearing rats. **Leptin** receptor density was doubled in the hypothalamus of **tumor** bearing rats, while binding affinity was decreased by 50%. These results suggest that peripheral **leptin** production is down-regulated, perhaps due to increased lipolysis in **tumor**-bearing rats. It appears that hypothalamic **leptin** systems up-regulate receptor numbers in response to decreased blood **leptin** level, however, the decrease in binding affinity may compensate for these alterations. Therefore, the influence of **leptin** on hypothalamic neuropeptide Y feeding systems may be minimal in anorectic **tumor**-bearing rats.

L4 ANSWER 74 OF 159 MEDLINE DUPLICATE 47

ACCESSION NUMBER: 1998192441 MEDLINE
DOCUMENT NUMBER: 98192441 PubMed ID: 9533757
TITLE: **Leptin** in relation to prostate **cancer** and benign prostatic hyperplasia.
AUTHOR: Lagiou P; Signorello L B; Trichopoulos D; Tzonou A; Trichopoulou A; Mantzoros C S
CORPORATE SOURCE: Department of Epidemiology and Harvard Center for Cancer Prevention, Harvard School of Public Health, Boston, MA 02115, USA.
CONTRACT NUMBER: 5T32CA09001-21 (NCI)
SOURCE: INTERNATIONAL JOURNAL OF CANCER, **(1998 Mar 30)** 76 (1) 25-8.
Journal code: GQU; 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980422
Last Updated on STN: 20000303
Entered Medline: 19980415

AB The aim of our study was to determine whether **leptin**, a hormone implicated in both energy-balance and reproductive function, is involved in the etiology of prostate **cancer** or benign prostatic hyperplasia (BPH). We compared the serum **leptin** levels of 43 cases of incident prostate **cancer**, 41 patients with BPH, and 48 healthy controls, all recruited in Athens, Greece. Multiple logistic regression modeling was used, with adjustment for age, height, body mass index, education, estradiol, testosterone, dihydrotestosterone, dehydroepiandrosterone sulfate, sex hormone-binding globulin and insulin like growth factor 1. Odds ratios per 4 ng/ml increment of **leptin** were 0.70 [95% confidence interval (CI) (0.32,1.55)] for prostate **cancer** and 1.06 [95% CI (0.67,1.67)] for BPH. After adjustment for body mass index, serum **leptin** levels were not significantly correlated with levels of any of the other hormones under study. **Leptin** levels are unlikely to affect the risk of either prostate

cancer or BPH substantially.

L4 ANSWER 75 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:21202 BIOSIS
DOCUMENT NUMBER: PREV199900021202
TITLE: Cranial irradiation in childhood induces **leptin** insensitivity.
AUTHOR(S): Brennan, Rahim; Blum, Eden; Shalet, S. M.
CORPORATE SOURCE: Christie Hosp. NHS Trust, Manchester UK
SOURCE: Hormone Research (Basel), (**Sept.**, **1998**) Vol. 50, No. SUPPL. 3, pp. 16.
Meeting Info.: 37th Annual Meeting of the European Society for Paediatric Endocrinology Florence, Italy September 24-27, 1998 European Society for Paediatric Endocrinology . ISSN: 0301-0163.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 76 OF 159 MEDLINE DUPLICATE 48
ACCESSION NUMBER: 2000442185 MEDLINE
DOCUMENT NUMBER: 20443537 PubMed ID: 10990130
TITLE: Genetics of visceral obesity and insulin resistance: relationship to non-insulin-dependent diabetes mellitus.
AUTHOR: Groop L
CORPORATE SOURCE: Department of Endocrinology, Lund University, Malmo, Sweden.
SOURCE: GROWTH HORMONE AND IGF RESEARCH, **(1998 Apr)** 8 Suppl B 9-14. Ref: 55
Journal code: DA2; 9814320. ISSN: 1096-6374.
PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20001004

L4 ANSWER 77 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:282399 BIOSIS
DOCUMENT NUMBER: PREV199800282399
TITLE: Effect of insulin at the **leptin** and TNF-alpha secretion in the interstitial fluid using the method of the open flow microperfusion.
AUTHOR(S): Sendlhofer, G. (1); Ellmerer, M.; Schaupp, L. (1); Wutte, A.; Krispler, W.; Trajanoski, Z.; Brunner, G.; Blum, W. F.; Yudkin, J. S.; Pieber, R. T. (1)
CORPORATE SOURCE: (1) Dep. Internal Med., Univ. Graz, Graz Austria
SOURCE: European Journal of Clinical Investigation, (**May**, **1998**) Vol. 28, No. SUPPL. 1, pp. A8.
Meeting Info.: 32nd Annual Scientific Meeting of the European Society for Clinical Investigation Cracow, Poland April 16-19, 1998 European Society for Clinical Investigation

. ISSN: 0014-2972.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 78 OF 159 CANCERLIT
ACCESSION NUMBER: 1998318449 CANCERLIT
DOCUMENT NUMBER: 98318449
TITLE: Endotoxin-induced alteration in the expression of **leptin** and beta3-adrenergic receptor in adipose tissue.
AUTHOR: Berkowitz D E; Brown D; Lee K M; Emala C; Palmer D; An Y; Breslow M
CORPORATE SOURCE: Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21287, USA.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, **(1998)**. 274 (6 Pt. 1):E992-7.
Journal code: 3U8. ISSN: 0002-9513.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDL; L; Priority Journals
LANGUAGE: English
OTHER SOURCE: MEDLINE 98318449
ENTRY MONTH: 199809
AB Cytokines, such as **tumor** necrosis factor (TNF) and interleukin-6, may contribute to the anorexia and cachexia of infection, **cancer**, and AIDS. The present study tests the hypothesis that endotoxin alters the expression of two key fat cell proteins, **leptin** and beta3-adrenergic receptor (beta3-AR), through a mechanism involving TNF-alpha. Increasing doses of Escherichia coli endotoxin (lipopolysaccharide, LPS) resulted in dose-dependent elevations of plasma **leptin** (maximal response approximately 7-fold, half-maximal effective dose of approximately 16 microg/100 g body wt) and white fat **leptin** mRNA in C3/HeOUJ mice. LPS also produced a large decrease in adipose tissue beta3-AR mRNA and a parallel reduction in beta-agonist-induced activation of adenylyl cyclase. Changes in plasma **leptin** and beta3-AR mRNA were preceded by an approximately threefold increase in white fat TNF mRNA. TNF administration resulted in changes similar to those seen with LPS. We conclude that endotoxemia results in an induction of **leptin** mRNA and a decrease in beta3-AR mRNA in adipose tissue, an effect that may be mediated by alterations in TNF-alpha.

L4 ANSWER 79 OF 159 CANCERLIT
ACCESSION NUMBER: 1998365321 CANCERLIT
DOCUMENT NUMBER: 98365321
TITLE: Advancing age and insulin resistance: role of plasma **tumor** necrosis factor-alpha.
AUTHOR: Paolisso G; Rizzo M R; Mazziotti G; Tagliamonte M R; Gambardella A; Rotondi M; Carella C; Giugliano D; Varricchio M; D'Onofrio F
CORPORATE SOURCE: Department of Geriatric Medicine and Metabolic Diseases, University of Napoli, 80138 Naples, Italy.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, **(1998)**. 275 (2 Pt. 1):E294-9.
Journal code: 3U8. ISSN: 0002-9513.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

FILE SEGMENT: MEDL; L; Priority Journals
LANGUAGE: English
OTHER SOURCE: MEDLINE 98365321
ENTRY MONTH: 199810
AB In 70 healthy subjects with a large age range, the relationships between plasma **tumor** necrosis factor-alpha (TNF-alpha) and body composition, insulin action, and substrate oxidation were investigated. In the cross-sectional study (n = 70), advancing age correlated with plasma TNF-alpha concentration (r = 0.64, P < 0.001) and whole body glucose disposal (WBGD; r= -0.38, P < 0.01). The correlation between plasma TNF-alpha and age was independent of sex and body fat (BF; r = 0.31, P < 0.01). Independent of age and sex, a significant relationship between plasma TNF-alpha and **leptin** concentration (r = 0.29, P < 0.02) was also found. After control for age, sex, BF, and waist-to-hip ratio (WHR), plasma TNF-alpha was still correlated with WBGD (r = -0.33, P < 0.007). Further correction for plasma free fatty acid (FFA) concentration made the latter correlation no more significant. In a multivariate analysis, a model made by age, sex, BF, fat- free mass, WHR, and plasma TNF-alpha concentrations explained 69% of WBGD variability with age (P < 0.009), BF (P < 0.006), fat-free mass (P < 0.005), and plasma TNF-alpha (P < 0.05) significantly and independently associated with WBGD. In the longitudinal study, made with subjects at the highest tertiles of plasma TNF-alpha concentration (n = 50), plasma TNF-alpha concentration predicted a decline in WBGD independent of age, sex, BF, WHR [relative risk (RR) = 2.0; 95% confidence intervals (CI) = 1.2-2.4]. After further adjustment for plasma fasting FFA concentration, the predictive role of fasting plasma TNF-alpha concentration on WBGD (RR = 1.2; CI = 0.8-1.5) was no more significant. In conclusion, our study demonstrates that plasma TNF-alpha concentration is significantly associated with advancing age and that it predicts the impairment in insulin action with advancing age.

L4 ANSWER 80 OF 159 CANCERLIT
ACCESSION NUMBER: 1998120540 CANCERLIT
DOCUMENT NUMBER: 98120540
TITLE: IL-1 beta mediates **leptin** induction during inflammation.
AUTHOR: Faggioni R; Fantuzzi G; Fuller J; Dinarello C A; Feingold K R; Grunfeld C
CORPORATE SOURCE: Metabolism Section, Veterans Affairs Medical Center, University of California, San Francisco 94121, USA.
CONTRACT NUMBER: DK-40990 (NIDDK)
DK-49448 (NIDDK)
AI-15614 (NIAID)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, **(1998)**. 274 (1 Pt. 2):R204-8.
Journal code: 3U8. ISSN: 0002-9513.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDL; L; Priority Journals
LANGUAGE: English
OTHER SOURCE: MEDLINE 98120540
ENTRY MONTH: 199803
AB Interleukins (IL) are key mediators of the host response to infection and inflammation. **Leptin** is secreted by adipose tissue and plays an

important role in the control of food intake. Administration of lipopolysaccharide (LPS), **tumor** necrosis factor (TNF), or IL-1 acutely increases **leptin** mRNA and protein levels. To investigate the role of IL-1 beta and IL-6 in **leptin** expression during inflammation, we used IL-1 beta-deficient (-/-) and IL-6 -/- mice. Mice were injected intraperitoneally with LPS or subcutaneously with turpentine, as models of systemic or local inflammation, respectively. In IL-1 beta +/+ mice, both LPS and turpentine increased **leptin** mRNA and circulating **leptin**. In contrast, neither LPS nor turpentine increased **leptin** levels in IL-1 beta -/- mice. In IL-6 +/+ or IL-6 -/- mice, turpentine increased **leptin** protein to comparable levels. We conclude that IL-1 beta is essential for **leptin** induction by both LPS and turpentine in mice, but IL-6 is not.

L4 ANSWER 81 OF 159 CANCERLIT
ACCESSION NUMBER: 1998399807 CANCERLIT
DOCUMENT NUMBER: 98399807
TITLE: **Leptin** causes body weight loss in the absence of in vivo activities typical of cytokines of the IL-6 family.
AUTHOR: Agnello D; Meazza C; Rowan C G; Villa P; Ghezzi P; Senaldi G
CORPORATE SOURCE: "Mario Negri" Institute for Pharmacological Research, 20157 Milan, Italy.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, **(1998)**. 275 (3 Pt. 2):R913-9. Journal code: 3U8. ISSN: 0002-9513.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDL; L; Priority Journals
LANGUAGE: English
OTHER SOURCE: MEDLINE 98399807
ENTRY MONTH: 199811
AB To investigate if **leptin** shares in vivo activities with interleukin (IL)-6 family cytokines, it was tested in normal mice for the ability, after a single injection, to induce the acute-phase protein serum amyloid A, to potentiate the induction by IL-1 of serum corticosterone and IL-6, and to inhibit the induction by lipopolysaccharide of serum **tumor** necrosis factor and, after seven daily injections, to cause body weight loss and to change peripheral blood cell counts. At a 0.5 mg/kg dose, **leptin** caused body weight loss but did not show any of the other activities above. At a dose of 5 mg/kg, which also caused body weight loss, **leptin** potentiated the induction by IL-1 of serum corticosterone and IL-6 but did not show any other activity. In addition to causing body weight loss, **leptin** shows only some of the in vivo activities typical of IL-6 family cytokines and only if used at a dose that exceeds the one sufficient to affect body weight. In vivo, **leptin** seems to chiefly control body weight and not inflammatory or hematopoietic processes.

L4 ANSWER 82 OF 159 MEDLINE
ACCESSION NUMBER: 97190626 MEDLINE
DOCUMENT NUMBER: 97190626 PubMed ID: 9038586
TITLE: Regulation of adipose cell number in man.
AUTHOR: Prins J B; O'Rahilly S

SOURCE: CLINICAL SCIENCE, **(1997 Jan)** 92 (1) 3-11. Ref: 101
Journal code: DIZ; 7905731. ISSN: 0143-5221.
PUB. COUNTRY: ENGLAND: United Kingdom
Editorial
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970321
Last Updated on STN: 19970321
Entered Medline: 19970307

AB 1. Adipose tissue mass is dependent on both the average volume and the number of its constituent adipocytes. Significant alteration in body mass involves alteration in both adipocyte volume and number. 2. Increases in adipocyte number occur via replication and differentiation of preadipocytes, a process which occurs throughout life. Decreases in adipocyte number occur via preadipocyte and adipocyte apoptosis, and possibly adipocyte dedifferentiation. 3. Overall regulation of adipose mass involves endocrine, paracrine and possibly autocrine systems. Hypothalamic centres appear to control appetite, metabolic rate and activity levels in a co-ordinated manner. Within the hypothalamus, known weight regulatory molecules include glucagon-like peptide-1, neuropeptide Y and **leptin**. **Leptin** is a major afferent signal from adipose tissue to the hypothalamus, providing information on overall adipose tissue mass. However, the precise means by which the hypothalamus signals to adipose tissue is less well understood. 4. In adipose tissue, known molecular regulators of adipose cell number include insulin, ligands for the peroxisome proliferator activated receptor-gamma, retinoids, corticosteroids and **tumour** necrosis factor-alpha. The net effect of these and other regulators is to effect a concerted alteration in adipocyte volume and number. This review largely focuses on the control of fat cell acquisition and loss and the influence of these processes on adipose tissue mass and regional distribution.

L4 ANSWER 83 OF 159 MEDLINE DUPLICATE 49
ACCESSION NUMBER: 97341153 MEDLINE
DOCUMENT NUMBER: 97341153 PubMed ID: 9195922
TITLE: **Leptin** receptor action in hepatic cells.
AUTHOR: Wang Y; Kuropatwinski K K; White D W; Hawley T S; Hawley R G; Tartaglia L A; Baumann H
CORPORATE SOURCE: Department of Molecular and Cellular Biology, Roswell Park Cancer Institute, Buffalo, New York 14263, USA.
CONTRACT NUMBER: CA26122 (NCI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, **(1997 Jun 27)** 272 (26) 16216-23.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970724
Last Updated on STN: 20000303
Entered Medline: 19970716

AB **Leptin**, an adipocyte-secreted hormone, is one of the central regulators of body weight homeostasis. In humans and rodents, two major forms of **leptin** receptors (OB-R) are expressed. The short form (OB-RS), considered to lack signaling capability, is detected in many organs. In contrast, OB-R long form (OB-RL) predominates in the hypothalamus, but is also present at low levels in peripheral tissues. Transient transfection experiments have demonstrated that OB-RL transduces an intracellular signaling similar to interleukin (IL)-6 type-cytokine receptors. To define the specificity by which OB-R induces genes and cooperates with signal transduction pathways utilized by other hormones and cytokines, rat and human hepatoma cell lines were generated which stably express human OB-RL. Hepatoma cell lines selected for appreciable levels of OB-RL mRNA display enhanced **leptin** binding and responded to **leptin** with an IL-6 receptor-like signaling that includes the activation of STAT proteins, induction of acute-phase plasma proteins, and synergism with IL-1 and **tumor** necrosis factor-alpha. A **leptin**-mediated recruitment of phosphatidylinositol 3-kinase to insulin receptor substrate-2 was also detected. However, no significant tyrosine phosphorylation of insulin receptor substrate-2 and modulation of the immediate cell response to insulin were observed. The data suggest that OB-RL action in hepatic cells is equivalent to that of IL-6 receptor. However, **leptin** does not play a specific role in muting insulin action on hepatoma cells and therefore may not contribute to the diabetic symptoms associated with obesity.

L4 ANSWER 84 OF 159 MEDLINE DUPLICATE 50

ACCESSION NUMBER: 97236848 MEDLINE
DOCUMENT NUMBER: 97236848 PubMed ID: 9079720
TITLE: Uptake of long chain free fatty acids is selectively up-regulated in adipocytes of Zucker rats with genetic obesity and non-insulin-dependent diabetes mellitus.
AUTHOR: Berk P D; Zhou S L; Kiang C L; Stump D; Bradbury M; Isola L M
CORPORATE SOURCE: Department of Medicine, Mount Sinai School of Medicine, New York, New York 10029, USA.
CONTRACT NUMBER: DK-26438 (NIDDK)
DK26687 (NIDDK)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, **(1997 Mar 28)** 272 (13) 8830-5.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970514
Last Updated on STN: 20000303
Entered Medline: 19970502

AB To examine whether fatty acid transport is abnormal in obesity, the kinetics of [3H]oleate uptake by hepatocytes, cardiac myocytes, and adipocytes from adult male Wistar (+/+), Zucker lean (fa/+) and fatty (fa/fa), and Zucker diabetic fatty (ZDF) rats were studied. A tissue-specific increase in oleate uptake was found in fa/fa and ZDF

adipocytes, in which the Vmax was increased 9-fold ($p < 0.005$) and 13-fold ($p < 0.001$), respectively. This increase greatly exceeded the 2-fold increase in the surface area of adipocytes from obese animals, and did not result from trans-stimulation secondary to increased lipolysis. Adipocyte **tumor** necrosis factor-alpha mRNA levels, assayed by Northern hybridization, increased in the order +/+ < fa/fa < ZDF. Oleate uptake was also studied in adipocytes from 20-24-day-old male +/+, fa/+, and fa/fa weanlings. These animals were not obese, and had equivalent plasma fatty acid and glucose levels. **Tumor** necrosis factor-alpha mRNA levels in +/+ and fa/fa cells also were similar. Nevertheless, Vmax was increased 2.9-fold ($p < 0.005$) in fa/fa compared +/+ cells. These studies indicate 1) that regulation of fatty acid uptake is tissue-specific and 2) that up-regulation of adipocyte fatty acid uptake is an early event in Zucker fa/fa rats. These findings are independent of the role of any particular fatty acid transporter. Adipocyte mRNA levels of three putative transporters, mitochondrial aspartate aminotransferase, fatty acid translocase, and fatty acid transporting protein (FATP) were also determined; mitochondrial aspartate aminotransferase and FATP mRNAs correlated strongly with fatty acid uptake.

L4 ANSWER 85 OF 159 MEDLINE DUPLICATE 51

ACCESSION NUMBER: 1998060964 MEDLINE
DOCUMENT NUMBER: 98060964 PubMed ID: 9398717
TITLE: **Tumor** necrosis factor increases serum **leptin** levels in humans.
AUTHOR: Zumbach M S; Boehme M W; Wahl P; Stremmel W; Ziegler R; Nawroth P P
CORPORATE SOURCE: Department of Medicine, University of Heidelberg, Germany.
SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, **(1997 Dec)** 82 (12) 4080-2.
Journal code: HRB; 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 20000303
Entered Medline: 19980113

AB **Leptin** is a pleiotropic hormone believed to regulate body weight. Its function in wasting during inflammatory disease in humans is unknown. We studied the effect of repeated **tumor** necrosis factor (TNF) infusion on serum **leptin** levels in six patients with solid **tumors**. TNF infusion on day 1 resulted in an increase in serum **leptin** levels from 3.1 (SEM +/- 0.28) ng/mL to 5.2 (SEM +/- 0.6) ng/mL after 12 h ($P < 0.001$). The serum levels returned to baseline within 24 h. Similar results were obtained when TNF was infused on subsequent days. The study shows that **leptin** serum levels are under control of TNF.

L4 ANSWER 86 OF 159 MEDLINE DUPLICATE 52
ACCESSION NUMBER: 97469960 MEDLINE
DOCUMENT NUMBER: 97469960 PubMed ID: 9329377
TITLE: **Leptin** concentrations in relation to body mass index and the **tumor** necrosis factor-alpha system in humans.
AUTHOR: Mantzoros C S; Moschos S; Avramopoulos I; Kaklamani V; Liolios A; Doulgerakis D E; Griveas I; Katsilambros N; Flier J S
CORPORATE SOURCE: Charles A. Dana Research Institute, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215, USA.
CONTRACT NUMBER: DK 28082 (NIDDK)
M01 RR01032 (NCRR)
SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, **(1997 Oct)** 82 (10) 3408-13.
Journal code: HRB; 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 20000303
Entered Medline: 19971117

AB The expression of **leptin**, an adipocyte-derived protein whose circulating levels reflect energy stores, can be induced by **tumor** necrosis factor (TNF)alpha in rodents, but an association between the TNF alpha system and **leptin** levels has not been reported in humans. To evaluate the potential association between serum **leptin** and the TNF alpha system, we measured the levels of soluble TNF alpha-receptor (sTNF alpha-R55), which has been validated as a sensitive indicator of activation of the TNF alpha system. We studied two groups: 1) 82 young healthy normal controls and 2) 48 patients with noninsulin dependent diabetes mellitus (NIDDM) and 24 appropriately matched controls. By simple regression analysis in controls, there was a strong positive association between **leptin** and 3 parameters: body mass index, sTNF alpha-R55, and insulin levels. In a multiple regression analysis model, **leptin** remained significantly and strongly associated with body mass index, and the association of **leptin** with both insulin and sTNF alpha-R55, although weakened, remained significant. Patients with NIDDM had **leptin** concentrations similar to controls of similar weight. Importantly, serum levels of sTNF alpha-R55 were also positively and independently associated with **leptin** in this group of diabetic subjects and matched controls. These data are consistent with the hypothesis that the TNF alpha system plays a role in regulating **leptin** levels in humans. Further elucidation of a possible role of the TNF alpha system in **leptin** expression and circulating levels may have important implications for our understanding of obesity and cachexia in humans.

L4 ANSWER 87 OF 159 MEDLINE DUPLICATE 53
ACCESSION NUMBER: 97430641 MEDLINE
DOCUMENT NUMBER: 97430641 PubMed ID: 9284748
TITLE: Interleukin 1 alpha increases serum **leptin**

concentrations in humans.

AUTHOR: Janik J E; Curti B D; Considine R V; Rager H C; Powers G C; Alvord W G; Smith J W 2nd; Gause B L; Kopp W C

CORPORATE SOURCE: Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892-1906, USA.

SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, **(1997 Sep)** 82 (9) 3084-6.
Journal code: HRB; 0375362. ISSN: 0021-972X.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971013
Last Updated on STN: 20000303
Entered Medline: 19971002

AB **Leptin**, the protein product of the ob gene, regulates appetite and body weight in animals. Endotoxin and cytokines, induced by endotoxin, interleukin (IL) 1 and **tumor** necrosis factor, increase expression of **leptin** in mice and hamsters. We measured serum **leptin** concentrations in patients with **cancer** before and after administration of recombinant human IL-1 alpha. Fourteen patients received IL-1 alpha at one of three dose levels (0.03, 0.1, or 0.3 microgram/kg.day) for 5 days. Serum **leptin** concentrations increased in all but two patients within 24 h after the first dose. The increase in **leptin** was correlated directly with IL-1 alpha dose ($P = 0.0030$). Despite continued administration of IL-1 alpha, serum **leptin** concentrations returned to pretreatment levels by day 5 of therapy. An increase in serum **leptin** concentrations may be one mechanism by which anorexia is induced by IL-1 alpha. However, tachyphylaxis of the **leptin** response suggests that other mechanisms also are involved.

L4 ANSWER 88 OF 159 MEDLINE DUPLICATE 54

ACCESSION NUMBER: 1998052580 MEDLINE
DOCUMENT NUMBER: 98052580 PubMed ID: 9389742

TITLE: **Tumor** necrosis factor-alpha contributes to obesity-related hyperleptinemia by regulating **leptin** release from adipocytes.

AUTHOR: Kirchgessner T G; Uysal K T; Wiesbrock S M; Marino M W; Hotamisligil G S

CORPORATE SOURCE: Bristol-Myers Squibb Co., Pharmaceutical Research Institute, Princeton, New Jersey 08543, USA.

CONTRACT NUMBER: 1P30 DK40561-04 (NIDDK)
2P30 DK36836 (NIDDK)

SOURCE: JOURNAL OF CLINICAL INVESTIGATION, **(1997 Dec 1)** 100 (11) 2777-82.
Journal code: HS7; 7802877. ISSN: 0021-9738.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 20000303
Entered Medline: 19980114

AB Cytokines, in particular **tumor** necrosis factor-alpha (TNF-alpha), have significant effects on energy metabolism and appetite although their mechanisms of action are largely unknown. Here, we examined whether TNF-alpha modulates the production of **leptin**, the recently identified fat-specific energy balance hormone, in cultured adipocytes and in mice. TNF-alpha treatment of 3T3-L1 adipocytes resulted in rapid stimulation of **leptin** accumulation in the media, with a maximum effect at 6 h. This stimulation was insensitive to cycloheximide, a protein synthesis inhibitor, but was completely inhibited by the secretion inhibitor brefeldin A, indicating a posttranslational effect. Treatment of mice with TNF-alpha also caused a similar increase in plasma **leptin** levels. Finally, in obese TNF-alpha-deficient mice, circulating **leptin** levels were significantly lower, whereas adipose tissue **leptin** was higher compared with obese wild-type animals. These data provide evidence that TNF-alpha can act directly on adipocytes to regulate the release of a preformed pool of **leptin**. Furthermore, they suggest that the elevated adipose tissue expression of TNF-alpha that occurs in obesity may contribute to obesity-related hyperleptinemia.

L4 ANSWER 89 OF 159 MEDLINE DUPLICATE 55

ACCESSION NUMBER: 1998052574 MEDLINE
DOCUMENT NUMBER: 98052574 PubMed ID: 9389736
TITLE: **Leptin** rapidly suppresses insulin release from insulinoma cells, rat and human islets and, in vivo, in mice.
AUTHOR: Kulkarni R N; Wang Z L; Wang R M; Hurley J D; Smith D M; Ghatei M A; Withers D J; Gardiner J V; Bailey C J; Bloom S R
CORPORATE SOURCE: Division of Endocrinology, Department of Metabolic Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0NN, United Kingdom.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, **(1997 Dec 1)** 100 (11) 2729-36.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 20000303
Entered Medline: 19980114

AB Obesity is associated with diabetes, and **leptin** is known to be elevated in obesity. To investigate whether **leptin** has a direct effect on insulin secretion, isolated rat and human islets and cultured insulinoma cells were studied. In all cases, mouse **leptin** inhibited insulin secretion at concentrations within the plasma range reported in humans. Insulin mRNA expression was also suppressed in the cultured cells and rat islets. The long form of the **leptin** receptor (OB-Rb) mRNA was present in the islets and insulinoma cell lines.
To determine the significance of these findings in vivo, normal fed mice were injected with two doses of **leptin**. A significant decrease in plasma insulin and associated rise in glucose concentration were observed. Fasted normal and **leptin** receptor-deficient db/db mice

showed no response to **leptin**. A dose of **leptin**, which mimicked that found in normal mice, was administered to **leptin** -deficient, hyperinsulinemic ob/ob mice. This caused a marked lowering of plasma insulin concentration and a doubling of plasma glucose. Thus, **leptin** has a powerful acute inhibitory effect on insulin secretion. These results suggest that the action of **leptin** may be one mechanism by which excess adipose tissue could acutely impair carbohydrate metabolism.

DUPLICATE 56

L4 ANSWER 90 OF 159 MEDLINE

ACCESSION NUMBER: 97397270 MEDLINE
DOCUMENT NUMBER: 97397270 PubMed ID: 9253331
TITLE: Glucocorticoid regulation of **leptin** synthesis and secretion in humans: elevated plasma **leptin** levels in Cushing's syndrome.
COMMENT: Comment in: J Clin Endocrinol Metab. 1998 Apr;83(4):1400
Comment in: J Clin Endocrinol Metab. 1998 May;83(5):1821-2
AUTHOR: Masuzaki H; Ogawa Y; Hosoda K; Miyawaki T; Hanaoka I; Hiraoka J; Yasuno A; Nishimura H; Yoshimasa Y; Nishi S; Nakao K
CORPORATE SOURCE: Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, Japan.
SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, **(1997 Aug)** 82 (8) 2542-7.
Journal code: HRB; 0375362. ISSN: 0021-972X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970908
Last Updated on STN: 20000303
Entered Medline: 19970828

AB **Leptin**, the obese (ob) gene product, is an adipocyte-derived satiety factor that is involved in the regulation of food ingestion and body weight. To investigate glucocorticoid regulation of **leptin** synthesis and secretion in humans, we measured plasma **leptin** levels in patients with Cushing's syndrome with adrenal or pituitary adenoma and in patients with iatrogenic Cushing's syndrome. Plasma **leptin** levels in patients with Cushing's syndrome were significantly elevated compared to those in nonobese healthy subjects and obese subjects without any metabolic or endocrine diseases at a given percentage of body fat by analysis of covariance. In patients with adrenal or pituitary adenoma, after the **tumor** resection, plasma **leptin** levels were reduced, with a concurrent decrease in plasma cortisol levels. With no significant changes in body weight, plasma **leptin** levels were also elevated significantly in lean healthy volunteers 24 h after the administration of 1 mg dexamethasone. Dexamethasone potently induced ob gene expression and **leptin** secretion in the organ culture of human adipose tissue. The data demonstrate that glucocorticoids act, at least in part, directly on the adipose tissue and increase **leptin** synthesis and secretion in humans.

DUPLICATE 57

L4 ANSWER 91 OF 159 MEDLINE

ACCESSION NUMBER: 1998052370 MEDLINE
DOCUMENT NUMBER: 98052370 PubMed ID: 9392477

TITLE: **Tumor** necrosis factor-alpha induces apoptosis of human adipose cells.

AUTHOR: Prins J B; Niesler C U; Winterford C M; Bright N A; Siddle K; O'Rahilly S; Walker N I; Cameron D P

CORPORATE SOURCE: Department of Medicine, University of Cambridge, Addenbrooke's Hospital, England, U.K..
jprins@hgmp.mrc.ac.uk

SOURCE: DIABETES, **(1997 Dec)** 46 (12) 1939-44.
Journal code: E8X; 0372763. ISSN: 0012-1797.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971223

AB **Tumor** necrosis factor-alpha (TNF-alpha) production by adipocytes is elevated in obesity, as shown by increased adipose tissue TNF-alpha mRNA and protein levels and by increased circulating concentrations of the cytokine. Furthermore, TNF-alpha has distinct effects on adipose tissue including induction of insulin resistance, induction of **leptin** production, stimulation of lipolysis, suppression of lipogenesis, induction of adipocyte dedifferentiation, and impairment of preadipocyte differentiation in vitro. Taken together, these effects all tend to decrease adipocyte volume and number and suggest a role for TNF-alpha in limiting increase in fat mass. The aim of the present study was to determine if TNF-alpha could induce apoptosis in human adipose cells, hence delineating another mechanism by which the cytokine could act to limit the development of, or extent of, obesity. Cultured human preadipocytes and mature adipocytes in explant cultures were exposed in vitro to human TNF-alpha at varying concentrations for up to 24 h. Apoptosis was assessed using morphological (histology, nuclear morphology following acridine orange staining, electron microscopy) and biochemical (demonstration of internucleosomal DNA cleavage by gel electrophoresis and of annexin V staining using immunocytochemistry) criteria. In control cultures, apoptotic indexes were between 0 and 2.3% in all experiments. In the experimental systems, TNF-alpha induced apoptosis in both preadipocytes and adipocytes, with indexes between 5 and 25%. Therefore, TNF-alpha induces apoptosis of human preadipocytes and adipocytes in vitro. In view of the major metabolic role of TNF-alpha in human adipose tissue, and the knowledge that adipose tissue is dynamic (with cell acquisition via preadipocyte replication/differentiation and cell loss via apoptosis), these findings describe a further mechanism whereby adipose tissue mass may be modified by TNF-alpha.

L4 ANSWER 92 OF 159 MEDLINE

ACCESSION NUMBER: 97426592 MEDLINE
DOCUMENT NUMBER: 97426592 PubMed ID: 9278578
TITLE: Obesity as a pleiotropic effect of gene action.
AUTHOR: Wolff G L
CORPORATE SOURCE: National Center for Toxicological Research, Food and Drug Administration, U.S. Department of Health and Human Services, Jefferson, AR 72079, USA.

SOURCE: JOURNAL OF NUTRITION, **(1997 Sep)** 127 (9) 1897S-1901S. Ref: 31
Journal code: JEV; 0404243. ISSN: 0022-3166.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971105
Last Updated on STN: 20000303
Entered Medline: 19971022

AB Obesity, an easily detected and quantifiable phenotypic endpoint, is often considered, colloquially, as a disease. However, the study of obesity in rodents suggests that it is merely a convenient indicator of diverse underlying metabolic and physiologic dysregulations, rather than a disease entity in itself. To illustrate this concept, the differences between the murine Lepob/Lepob and Avy/- "obesity" syndromes are delineated. In both syndromes, pleiotropic effects of single mutations play a major role in altering the homeostatic regulation of energy metabolism and a myriad of extra- and intracellular processes in a diversity of tissues and cell types. The Lepob/Lepob syndrome mimics juvenile-onset obesity, whereas the Avy/- syndrome resembles maturity-onset obesity. The Avy/- syndrome has its basis in overabundance of agouti protein, whereas the Lepob/Lepob syndrome results from a lack of active **leptin** hormone. Lepob/Lepob mice have a smaller lean body mass, whereas Avy/- mice have a larger lean body mass than their respective lean siblings. Lepob/Lepob mice have fewer lung and mammary **tumors** than their lean Lep/- littermates, and Avy/- develop more mammary and lung **tumors** than their lean A/- or a/a siblings. Lepob/Lepob mice are infertile or sterile, whereas Avy/- mice are fertile. Thus, although adult Lepob/Lepob and Avy/- mice are both obese, many of the other morphologic and physiologic attributes of one mutant are diametrically opposite to those of the other.

L4 ANSWER 93 OF 159 MEDLINE DUPLICATE 58

ACCESSION NUMBER: 1998049615 MEDLINE
DOCUMENT NUMBER: 98049615 PubMed ID: 9388184
TITLE: Specific inhibition of Stat3 signal transduction by PIAS3.
AUTHOR: Chung C D; Liao J; Liu B; Rao X; Jay P; Berta P; Shuai K
CORPORATE SOURCE: Department of Biological Chemistry, University of California, Los Angeles, CA 90095, USA.
CONTRACT NUMBER: AI39612 (NIAID)
T32CA09056 (NCI)
SOURCE: SCIENCE, **(1997 Dec 5)** 278 (5344) 1803-5.
Journal code: UJ7; 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-H58757

ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971219

AB The signal transducer and activator of transcription-3 (Stat3) protein is activated by the interleukin 6 (IL-6) family of cytokines, epidermal growth factor, and **leptin**. A protein named PIAS3 (protein inhibitor of activated STAT) that binds to Stat3 was isolated and characterized. The association of PIAS3 with Stat3 in vivo was only observed in cells stimulated with ligands that cause the activation of Stat3. PIAS3 blocked the DNA-binding activity of Stat3 and inhibited Stat3-mediated gene activation. Although Stat1 is also phosphorylated in response to IL-6, PIAS3 did not interact with Stat1 or affect its DNA-binding or transcriptional activity. The results indicate that PIAS3 is a specific inhibitor of Stat3.

L4 ANSWER 94 OF 159 MEDLINE DUPLICATE 59
ACCESSION NUMBER: 97431554 MEDLINE
DOCUMENT NUMBER: 97431554 PubMed ID: 9287059
TITLE: Targeted disruption of the **tumor** necrosis factor-alpha gene: metabolic consequences in obese and nonobese mice.
AUTHOR: Ventre J; Doebber T; Wu M; MacNaul K; Stevens K; Pasparakis M; Kollias G; Moller D E
CORPORATE SOURCE: Department of Molecular Endocrinology, Merck Research Laboratories, Rahway, New Jersey 07065, USA.
SOURCE: DIABETES, **(1997 Sep)** 46 (9) 1526-31.
Journal code: E8X; 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19971008
Last Updated on STN: 19971008
Entered Medline: 19970925

AB To address the hypothesis that **tumor** necrosis factor (TNF)-alpha has a role in obesity-associated insulin resistance or the regulation of in vivo lipid metabolism, mice with targeted disruption of the TNF-alpha gene were generated and studied. The absence of TNF-alpha protein in TNF-null (-/-) mice was confirmed. Lean or obese (gold-thioglucose [GTG]-injected) homozygous (-/-) mice were compared with lean or obese age- and sex-matched wild-type (+/+) mice derived from the same line at 13, 19, and 28 weeks of age. The following parameters were significantly affected in lean -/- versus +/+ mice: Body weight was not affected until week 28 (decreased by 14%); epididymal fat pad weight also decreased (25%) at this time, as did percentage body fat (16%), while percentage body protein was increased 13%. Fed plasma insulin levels decreased 47% (28 weeks), triglyceride levels decreased (all three ages; maximum 35% at 19 weeks), and fed plasma **leptin** decreased 33% (28 weeks). Fasting glucose was slightly (10%) reduced, but the glucose response to an oral glucose tolerance test (OGTT) was not affected. There was a trend (NS) toward increased total adipose tissue lipoprotein lipase in -/- versus +/+ mice. GTG-treatment resulted in obese -/- and +/+ mice with equal mean body weights (42 and 58% increased weight versus lean mice). The following

parameters were significantly different in obese -/- mice: fasting plasma glucose decreased 13% (28 weeks), fed plasma insulin decreased 67% (28 weeks), and insulin response to OGTT was decreased by 50%. For both groups of obese mice, glucose levels during the OGTT were substantially increased compared with those in lean mice; however, mean stimulated glucose levels were 20% lower in obese -/- versus +/+ mice. We conclude 1) that TNF-alpha functions to regulate plasma triglycerides and body adiposity and 2) that although TNF-alpha contributes to reduced insulin sensitivity in older or obese mice, the absence of TNF-alpha is not sufficient to substantially protect against insulin resistance in the GTG hyperphagic model of rodent obesity.

L4 ANSWER 95 OF 159 MEDLINE DUPLICATE 60

ACCESSION NUMBER: 97431543 MEDLINE
DOCUMENT NUMBER: 97431543 PubMed ID: 9287048
TITLE: The TNF-alpha gene Nco I polymorphism influences the relationship among insulin resistance, percent body fat, and increased serum **leptin** levels.
AUTHOR: Fernandez-Real J M; Gutierrez C; Ricart W; Casamitjana R; Fernandez-Castaner M; Vendrell J; Richart C; Soler J
CORPORATE SOURCE: Department of Endocrinology, University Hospital of Girona Dr. Josep Trueta, Spain.
SOURCE: DIABETES, **(1997 Sep)** 46 (9) 1468-72.
Journal code: E8X; 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19971008
Last Updated on STN: 20000303
Entered Medline: 19970925

AB **Tumor** necrosis factor-alpha (TNF-alpha), acting as a modulator of gene expression in adipocytes, is implicated in the development of insulin resistance and obesity. The aim of this study was to investigate whether the Nco I polymorphism of the TNF-alpha gene influences the relationship among insulin resistance, percent body fat, and serum **leptin** levels. A sample of 38 subjects (19 men, mean age 36.2 +/- 1.9 years, BMI 28.8 +/- 1.2 kg/m2, range 22.2-35.7; and 19 women, age 34.9 +/- 1.4 years, BMI 28.1 +/- 0.8 kg/m2, range 19-37.9) was divided into two groups on the basis of the Nco I genotype. Twenty-three subjects were (+/+) homozygotes for the presence of the Nco I restriction site that is associated with a guanine at position -308 of the TNF-alpha promoter. Of the other subjects, 12 were (+/-) heterozygotes and 3 (-/-) homozygotes for the absence of the restriction site, resulting from a guanine-to-adenine substitution at position -308 of the TNF-alpha promoter. This substitution (termed TNF-2) leads to higher rate of transcription of TNF-alpha than the wild-type allele TNF-1 in vitro. TNF-1 (+/+) and TNF-2 (+/- and -/-) groups of subjects were comparable in sex, age, BMI, waist-to-hip ratio, and several skinfold measurements. Basal serum insulin was greater (14.2 +/- 2 vs. 9.2 +/- 0.9 mU/l, P = 0.041) in the TNF-2 group in the presence of comparable serum glucose concentration.

The integrated area under the curve of serum insulin concentrations, measured in response to a 75-g oral glucose challenge, and the percent body fat, measured by bioelectric impedance, were significantly increased in TNF-2 subjects (226.8 +/- 33 vs. 139.4 +/- 17.8 mU/l, P = 0.032; 33.6 +/- 2.8 vs. 24.9 +/- 2%, P = 0.01). TNF-2 subjects also showed a decreased insulin sensitivity index, as determined by the frequently sampled intravenous glucose tolerance test with minimal model analysis (1.9 +/- 0.4 vs. 3.05 +/- 0.3 min(-1) x mU(-1) x l(-1), P = 0.03). These differences were more marked among women. Paralleling the known relationship between insulin and **leptin** levels, serum **leptin** concentration was clearly increased in the TNF-2 group (19.6 +/- 3.4 vs. 11.1 +/- 1.5 ng/ml, P = 0.03). Therefore, (+/-) heterozygotes and (-/-) homozygotes may be more susceptible to developing insulin resistance and increased percent body fat. Results of the present study suggest that TNF-alphaNco I polymorphism may exacerbate the alterations in **leptin** levels normally found among insulin-resistant subjects.

L4 ANSWER 96 OF 159 MEDLINE DUPLICATE 61

ACCESSION NUMBER: 1998231654 MEDLINE
DOCUMENT NUMBER: 98231654 PubMed ID: 9570135
TITLE: IL-6-regulated transcription factors.
AUTHOR: Akira S
CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, Japan.
SOURCE: INTERNATIONAL JOURNAL OF BIOCHEMISTRY AND CELL BIOLOGY, **(1997 Dec)** 29 (12) 1401-18. Ref: 158
Journal code: CDK; 9508482. ISSN: 1357-2725.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980529
Last Updated on STN: 19980529
Entered Medline: 19980521

AB Through the cloning of two transcription factors named NF-IL6 and STAT3/APRF, two types of IL-6 signal transduction pathways from the cell surface to the nucleus have been revealed. NF-IL6 is phosphorylated and activated by a Ras-dependent MAP kinase cascade, while STAT3/APRF is directly tyrosine-phosphorylated by JAK kinases that associate with the cytoplasmic portion of the receptor, and translocates to the nucleus and activates transcription (JAK-STAT pathway). STAT3 is also tyrosine phosphorylated in response to epidermal growth factor (EGF), granulocyte colony-stimulating factor (G-CSF), **leptin** and other IL-6-type cytokines including ciliary neurotrophic factor (CNTF), oncostatin M and **leukemia** inhibitory factor (LIF). Mice deficient in the genes for NF-IL6 and STAT3 were generated. NF-IL6 mice were highly susceptible to facultative intracellular bacteria owing to ineffective killing of the pathogens by the macrophages. Futhermore, the **tumor** cytotoxicity of macrophages from NF-IL6 KO mice was severely impaired. These results demonstrate a crucial role of NF-IL6 in macrophage bactericidal and tumoricidal activities. The target disruption of STAT3 resulted in embryonic lethality prior to gastrulation, demonstrating that STAT3 is essential for the early development of mouse embryos.

L4 ANSWER 97 OF 159 MEDLINE DUPLICATE 62
ACCESSION NUMBER: 1998057854 MEDLINE
DOCUMENT NUMBER: 98057854 PubMed ID: 9396072
TITLE: **Leptin**: a potent inhibitor of insulin secretion.
AUTHOR: Fehmann H C; Peiser C; Bode H P; Stamm M; Staats P; Hedetoft C; Lang R E; Goke B
CORPORATE SOURCE: Department of Medicine, Philipps-University of Marburg, Germany.
SOURCE: PEPTIDES, **(1997)** 18 (8) 1267-73.
Journal code: PA7; 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980217
Last Updated on STN: 20000303
Entered Medline: 19980130

AB The hormone **leptin** is expressed and secreted by the adipose tissue and impacts on the central nervous system. **Leptin** is involved in the regulation of energy balance, satiety, and body composition. The lack of active **leptin** results in obesity, high food intake, hyperglycemia, and hyperinsulinemia. We present data supporting effects of **leptin** on the endocrine pancreas. We found the **leptin** receptor to be expressed in insulin- and glucagon-secretin cells derived from mouse, hamster, and rat pancreas. In the isolated perfused rat pancreas **leptin** is a potent inhibitor of basal and glucose-induced insulin secretion, especially during the first phase of the insulin response. At isolated mouse islets and insulin-secreting INS-1 cells **leptin** reduced promptly and persistently the intracellular Ca2+ levels. Cytoplasmic Ca2+ oscillation amplitude was decreased and the oscillation frequency increased. These findings suggest functional active receptors for **leptin** on insulin-secreting B-cells. Therefore, **leptin** is a metabolic hormone and not only a signal to the brain indicating filled fat stores. Our data suggest that **leptin** is also a signal back to the endocrine pancreas that no more insulin is required to replenish fat stores. Thus, an "adipo-insular axis" operating with two arms exists: insulin and glucagon are signals to the adipocyte. This releases **leptin**, which could be the mediator of the respective feedback to the pancreas. A defective **leptin** suppression of insulin secretion could contribute to hyperinsulinemia and disturbances of glucose metabolism.

L4 ANSWER 98 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:281546 BIOSIS
DOCUMENT NUMBER: PREV199799580749
TITLE: **Leptin** modulates insulin secretion from rat insulinoma cells.
AUTHOR(S): Jasper, M. S.; Koo, L. J.; Kapla, L. M.
CORPORATE SOURCE: Gastrointestinal Unit, Mass. Gen. Hosp. Harv. Medical Sch., Boston, MA USA
SOURCE: Gastroenterology, (1997) Vol. 112, No. 4 SUPPL., pp. A1158.
Meeting Info.: Digestive Disease Week and the 97th Annual

Meeting of the American Gastroenterological Association
Washington, D.C., USA May 11-14, 1997
ISSN: 0016-5085.

DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

DUPLICATE 63

L4 ANSWER 99 OF 159 MEDLINE
ACCESSION NUMBER: 97309270 MEDLINE
DOCUMENT NUMBER: 97309270 PubMed ID: 9166685
TITLE: **Leptin** suppression of insulin secretion by the activation of ATP-sensitive K+ channels in pancreatic beta-cells.
AUTHOR: Kieffer T J; Heller R S; Leech C A; Holz G G; Habener J F
CORPORATE SOURCE: Laboratory of Molecular Endocrinology, Massachusetts General Hospital, Harvard Medical School, Boston 02114, USA.
SOURCE: DIABETES, **(1997 Jun)** 46 (6) 1087-93.
Journal code: E8X; 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 20000303
Entered Medline: 19970619

AB In the genetic mutant mouse models ob/ob or db/db, **leptin** deficiency or resistance, respectively, results in severe obesity and the development of a syndrome resembling NIDDM. One of the earliest manifestations in these mutant mice is hyperinsulinemia, suggesting that **leptin** may normally directly suppress the secretion of insulin. Here, we show that pancreatic islets express a long (signal-transducing) form of **leptin**-receptor mRNA and that beta-cells bind a fluorescent derivative of **leptin** (Cy3-**leptin**). The expression of **leptin** receptors on insulin-secreting beta-cells was also visualized utilizing antisera generated against an extracellular epitope of the receptor. A functional role for the beta-cell **leptin** receptor is indicated by our observation that **leptin** (100 ng/ml) suppressed the secretion of insulin from islets isolated from ob/ob mice. Furthermore, **leptin** produced a marked lowering of [Ca2+]i in ob/ob beta-cells, which was accompanied by cellular hyperpolarization and increased membrane conductance. Cell-attached patch measurements of ob/ob beta-cells demonstrated that **leptin** activated ATP-sensitive potassium channels (K(ATP)) by increasing the open channel probability, while exerting no effect on mean open time. These effects were reversed by the sulfonylurea tolbutamide, a specific inhibitor of K(ATP). Taken together, these observations indicate an important physiological role for **leptin** as an inhibitor of insulin secretion and lead us to propose that the failure of **leptin** to inhibit insulin secretion from the beta-cells of ob/ob and db/db mice may explain, in part, the development of hyperinsulinemia, insulin resistance, and the progression to NIDDM.

DUPLICATE 64

L4 ANSWER 100 OF 159 MEDLINE
ACCESSION NUMBER: 97433064 MEDLINE
DOCUMENT NUMBER: 97433064 PubMed ID: 9288733

TITLE: Nonadipose tissue production of **leptin**: **leptin** as a novel placenta-derived hormone in humans.

COMMENT: Comment in: Nat Med. 1997 Sep;3(9):952-3

AUTHOR: Masuzaki H; Ogawa Y; Sagawa N; Hosoda K; Matsumoto T; Mise H; Nishimura H; Yoshimasa Y; Tanaka I; Mori T; Nakao K

CORPORATE SOURCE: Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, Japan.

SOURCE: NATURE MEDICINE, **(1997 Sep)** 3 (9) 1029-33.
Journal code: CG5; 9502015. ISSN: 1078-8956.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199710

ENTRY DATE: Entered STN: 19971105
Last Updated on STN: 20000303
Entered Medline: 19971023

AB **Leptin** is a circulating hormone that is expressed abundantly and specifically in the adipose tissue. It is involved in the regulation of energy homeostasis, as well as the neuroendocrine and reproductive systems. Here, we demonstrate production of **leptin** by nonadipose tissue, namely, placental trophoblasts and amnion cells from uteri of pregnant women. We show that pregnant women secrete a considerable amount of **leptin** from the placenta into the maternal circulation as compared with nonpregnant obese women. **Leptin** production was also detected in a cultured human choriocarcinoma cell line, BeWo cells, and was augmented during the course of forskolin-induced differentiation of cytotrophoblasts into syncytiotrophoblasts. Plasma **leptin** levels were markedly elevated in patients with hydatidiform mole or choriocarcinoma and were reduced after surgical treatment or chemotherapy.

Leptin is also produced by primary cultured human amnion cells and is secreted into the amniotic fluid. The present study provides evidence for **leptin** as a novel placenta-derived hormone in humans and suggests the physiologic and pathophysiologic significance of **leptin** in normal pregnancy and gestational trophoblastic neoplasms.

L4 ANSWER 101 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1997:280976 BIOSIS

DOCUMENT NUMBER: PREV199799580179

TITLE: Role of **leptin** in regulation of body mass in Crohn's disease.

AUTHOR(S): Klapproth, J.-M.; James, S. P. (1); Dewoody, K. L.; Shealy, D.; Greenwald, B. D.; Group, Crohn's Disease Ca2 Study

CORPORATE SOURCE: (1) Centocor Inc., Malvern, PA USA

SOURCE: Gastroenterology, (1997) Vol. 112, No. 4 SUPPL., pp. A1015.
Meeting Info.: Digestive Disease Week and the 97th Annual Meeting of the American Gastroenterological Association Washington, D.C., USA May 11-14, 1997
ISSN: 0016-5085.

DOCUMENT TYPE: Conference; Abstract

LANGUAGE: English

L4 ANSWER 102 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1998:69560 BIOSIS
DOCUMENT NUMBER: PREV199800069560
TITLE: **Leptin** inhibits growth-factor-induced cell proliferation.
AUTHOR(S): Rubinstein, M.; Barkan, D.; Cohen, B.; Novick, D.
CORPORATE SOURCE: Weizmann Inst. Science, Rehovot 76100 Israel
SOURCE: Cytokine, (**Nov.**, **1997**) Vol. 9, No. 11, pp. 953. Meeting Info.: Fifth Annual Conference of the International Cytokine Society Lake Tahoe, Nevada, USA November 9-13, 1997 International Cytokine Society . ISSN: 1043-4666.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 103 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:487558 BIOSIS
DOCUMENT NUMBER: PREV199799786761
TITLE: Genetics of human obesity: Research directions.
AUTHOR(S): Bray, George (1); Bouchard, Claude
CORPORATE SOURCE: (1) Pennington Biomed. Res. Cent., Baton Rouge, LA 70808-4124 USA
SOURCE: FASEB Journal, (1997) Vol. 11, No. 12, pp. 937-945. ISSN: 0892-6638.
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
AB Rapid strides in understanding the physiology controlling energy or nutrient intake and energy expenditure have complemented the search for the genetic basis of obesity. Several single gene defects are known that produce obesity in animals. All of these have been cloned within the past 4 years, providing a rich new base for understanding obesity. Since obesity is likely to be "multifactorial," a number of laboratories have used the quantitative trait locus (QTL) technique of genome scanning to identify candidate genomic regions and, eventually, genes that may influence body weight and body fat. So far, 18 QTLs have been identified in association with crossbreeding strains of mice or rats with variable susceptibility to obesity. A number of mendelian disorders are known to exist in humans, but no specific genes have yet been identified for them. The potential for inserting new genetic material into mammals has produced numerous transgenic mice with increased or decreased quantities of body fat. These models will provide a continuing source of new insights into obesity. Several areas in the human genome have been linked to the development of obesity. Among the candidate genes with evidence of linkage to body fat are TNF-alpha, adenosine deaminase, and melanocortin-3 receptor. The new insights described above have invigorated the pharmaceutical industry to increase their efforts for new drug development aimed at the growing problem of obesity.

DUPLICATE 65

L4 ANSWER 104 OF 159 MEDLINE
ACCESSION NUMBER: 1998144651 MEDLINE
DOCUMENT NUMBER: 98144651 PubMed ID: 9483657
TITLE: Food, obesity and non-insulin-dependent diabetes: are there molecular links?.
AUTHOR: Prins J B

CORPORATE SOURCE: Department of Medicine, University of Cambridge, Addenbrooke's Hospital.
SOURCE: PROCEEDINGS OF THE NUTRITION SOCIETY, **(1997 Nov)** 56 (3) 889-98. Ref: 93
Journal code: PW6; 7505881. ISSN: 0029-6651.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980407
Last Updated on STN: 20000303
Entered Medline: 19980323

L4 ANSWER 105 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:280457 BIOSIS
DOCUMENT NUMBER: PREV199799579660
TITLE: **Leptin** dysregulation in Africans with 'slim disease.
AUTHOR(S): Kelly, P. (1); Ballinger, A.; Luo, N.; Pobe, J. O. M.; Farthing, M. J. G.
CORPORATE SOURCE: (1) DDRC, St. Bartholomew's Royal London Sch. Med. Dentistry, London UK
SOURCE: Gastroenterology, (1997) Vol. 112, No. 4 SUPPL., pp. A885.
Meeting Info.: Digestive Disease Week and the 97th Annual Meeting of the American Gastroenterological Association Washington, D.C., USA May 11-14, 1997
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L4 ANSWER 106 OF 159 MEDLINE DUPLICATE 66
ACCESSION NUMBER: 97278979 MEDLINE
DOCUMENT NUMBER: 97278979 PubMed ID: 9133556
TITLE: Production of plasminogen activator inhibitor 1 by human adipose tissue: possible link between visceral fat accumulation and vascular disease.
AUTHOR: Alessi M C; Peiretti F; Morange P; Henry M; Nalbone G; Juhan-Vague I
CORPORATE SOURCE: CJF, Institut National de la Sante et de la Recherche Medicale (INSERM), Laboratoire d'Hematologie, Marseille, France.
SOURCE: DIABETES, **(1997 May)** 46 (5) 860-7.
Journal code: E8X; 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970609
Last Updated on STN: 19970609
Entered Medline: 19970528

AB Plasminogen activator inhibitor type 1 (PAI-1) contributes to the pathogenesis of atherothrombosis. Its plasma level is strongly correlated with parameters that define the insulin resistance syndrome, in particular

with BMI and visceral accumulation of body fat, suggesting that PAI-1 may be an adipose tissue-derived circulating peptide. The present study was designed to investigate PAI-1 expression by human adipose tissue and its different cellular fractions. Special interest has been paid to the amount of PAI-1 antigen produced by omental versus subcutaneous fat. PAI-1 protein detected by immunolocalization was present at the stromal and adipocyte levels. PAI-1 mRNA was detected in stromal vascular cells freshly isolated and under culture conditions. It was also detected in whole adipose tissue and adipocyte fraction under culture conditions. The mRNA signal from the adipocyte fraction was detected as early as 2 h of incubation. The increase in PAI-1 mRNA was followed by an increase in PAI-1 antigen in the conditioned medium that was suppressed by treatment with cycloheximide. Transforming growth factor-beta1 significantly increased PAI-1 antigen production by the adipocyte fraction, whereas **tumor** necrosis factor-alpha did not have any effect. Interestingly, after 5 h of incubation, omental tissue explants produced significantly more PAI-1 antigen than did subcutaneous tissue from the same individual, whereas similar production of **leptin** by the two territories was observed. These results strongly suggest that human adipose tissue, in particular visceral tissue, can be an important contributor to the elevated plasma PAI-1 levels observed in central obesity.

L4 ANSWER 107 OF 159 MEDLINE DUPLICATE 67
ACCESSION NUMBER: 97472300 MEDLINE
DOCUMENT NUMBER: 97472300 PubMed ID: 9325180
TITLE: Rat insulinoma-derived pancreatic beta-cells express a functional **leptin** receptor that mediates a proliferative response.
AUTHOR: Islam M S; Morton N M; Hansson A; Emilsson V
CORPORATE SOURCE: The Rolf Luft Centre for Diabetes Research, Department of Molecular Medicine, Karolinska Institute, Stockholm, Sweden.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1997 Sep 29)** 238 (3) 851-5.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971027

AB In addition to its interaction at hypothalamic sites to affect feeding and energy expenditure, **leptin** has been shown to exhibit a proliferative response in erythropoietic cells. The functional **leptin** receptor is also present in pancreatic islets and we now demonstrate that a commonly used clonal insulin secreting beta-cell line, RINm5F, expresses high levels of the Ob-Rb mRNA. **Leptin** causes an increase in tyrosine phosphorylation of a number of intracellular proteins and a dose related (10 nM-200 nM) increase in expression of the immediate-early gene, c-fos. This precedes a **leptin** induced proliferative response in serum-deprived RINm5F cells, which suggests that **leptin** might be involved in the complex regulation of

proliferation of the pancreatic beta-cell.

L4 ANSWER 108 OF 159 MEDLINE DUPLICATE 68
ACCESSION NUMBER: 97312499 MEDLINE
DOCUMENT NUMBER: 97312499 PubMed ID: 9168940
TITLE: Demonstration of a **leptin** binding factor in human serum.
AUTHOR: Diamond F B Jr; Eichler D C; Duckett G; Jorgensen E V; Shulman D; Root A W
CORPORATE SOURCE: Department of Pediatric, University of South Florida, College of Medicine, Tampa 33612, USA.. fdiamond@allkids.edu
CONTRACT NUMBER: K08 DK 01980 (NIDDK)
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1997 Apr 28)** 233 (3) 818-22.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970716
Last Updated on STN: 20000303
Entered Medline: 19970630

AB Serum **leptin** levels are elevated in subjects with exogenous obesity, indicating that obesity is associated with **leptin** resistance. Since in man no abnormalities have yet been found in either the genes for **leptin** or its receptor, the mechanism of **leptin** resistance in obesity remains unknown. To determine if resistance might be related to **leptin** binding by a serum component, we assessed the carrier status of **leptin** in serum. The presence of a specific **leptin** binding factor in human serum has been established by (1) demonstrating [125I]-**leptin** binding to a serum component that is saturable and specifically displaceable only by unlabeled **leptin** and not by human growth hormone, pork insulin, insulin-like growth factors I and II, luteinizing or follicle stimulating hormones, transforming growth factor-beta 1, interleukin-6, or **leukemia** inhibiting factor; (2) fractionating the **leptin** bound serum complex and the serum **leptin** binding component on a molecular sieving column revealing a mass of approximately 450 kDa; and (3) identifying an inverse correlation between the concentration of serum **leptin** and the quantity of the **leptin** binding component. It is suggested that binding of **leptin** by this serum component may influence the physiologic response to **leptin**.

L4 ANSWER 109 OF 159 MEDLINE DUPLICATE 69
ACCESSION NUMBER: 97420203 MEDLINE
DOCUMENT NUMBER: 97420203 PubMed ID: 9274707
TITLE: **Leptin** levels do not change acutely with food administration in normal or obese subjects, but are negatively correlated with pituitary-adrenal activity.
AUTHOR: Korbonits M; Trainer P J; Little J A; Edwards R; Kopelman P G; Besser G M; Svec F; Grossman A B
CORPORATE SOURCE: Department of Endocrinology, St. Bartholomew's Hospital, London, UK.
SOURCE: CLINICAL ENDOCRINOLOGY, **(1997 Jun)** 46 (6) 751-7.

Journal code: DCI; 0346653. ISSN: 0300-0664.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970926
Last Updated on STN: 20000303
Entered Medline: 19970915

AB BACKGROUND: **Leptin** is a peptide secreted by white adipose tissue which has been shown to have a major influence on body weight regulation, while animal studies have revealed widespread interconnections between **leptin** and other endocrine systems, especially with insulin. However, its acute regulation has been little studied in the human. We have therefore investigated the effect of a 1000 kcal meal and fasting on the levels of **leptin**, insulin and cortisol, in both normal and obese subjects. SUBJECTS AND DESIGN: We have studied the effect of food and fasting on circulating **leptin** levels in 20 subjects of normal body mass index (BMI range 18-25) and in a group of 12 moderately-severely obese subjects (BMI range 34-61). We also studied the effect of food and fasting in a patient both before and after the successful removal of a pancreatic insulinoma as a model of excess insulin secretion. RESULTS: Mean **leptin** levels were significantly higher in the obese than in the lean group (42.7 +/- 3.41 vs 5.35 +/- 1.55 micrograms/l, mean +/- SEM; $P < 0.001$), and showed a positive correlation with body mass index ($r = +0.71$; $P < 0.001$). Frequent (every 20 minutes) sampling for 3 hours after food did not show any acute changes in circulating **leptin** levels. On the fasting day we observed a small but significant fall in circulating **leptin** levels in the last 4 hours of a 20-hour fast in our subjects as a group (92 +/- 0.03% of basal, $P = 0.03$); however, in the lean subjects the fall was greater (86 +/- 0.04% of basal, $P = 0.02$) than in the obese, where it did not reach statistical significance (96 +/- 0.05% of basal). Pre-meal and peak insulin levels showed a positive correlation with circulating mean **leptin** levels ($r = +0.65$; $P < 0.001$ and $r = +0.78$; $P < 0.001$, respectively) in all subjects, while pre-meal and peak serum cortisol levels showed an inverse relation with **leptin** levels ($r = -0.53$; $P = 0.002$ and $r = -0.41$; $P = 0.02$, respectively); this effect was independent of BMI in the obese subjects. In the patient with the insulinoma the markedly elevated insulin and **leptin** levels measured before the operation returned to normal after removal of the **tumour**, in accord with reports of experimental animal data that long-term insulin excess per se is associated with increased circulating **leptin** concentrations. CONCLUSION: **Leptin** is a robust indicator of BMI and insulin levels, both basal and stimulated, but does not change acutely following food. Fasting causes a proportionately greater decline in **leptin** levels in lean subjects than in obese subjects. Circulating **leptin** is inversely correlated with the activity of the hypothalamo-pituitary-adrenal axis: whether this is a direct influence of **leptin** on hypothalamo-pituitary-adrenal activity, or whether both are indirect indicators of body fat stores, requires further investigation.

L4 ANSWER 110 OF 159 MEDLINE DUPLICATE 70
ACCESSION NUMBER: 97465613 MEDLINE
DOCUMENT NUMBER: 97465613 PubMed ID: 9326333

TITLE: Recessive inheritance of obesity in familial non-insulin-dependent diabetes mellitus, and lack of linkage to nine candidate genes.

AUTHOR: Hasstedt S J; Hoffman M; Leppert M F; Elbein S C

CORPORATE SOURCE: Department of Human Genetics, University of Utah, Salt Lake City 84112-5330, USA.. sandy@sapporo.genetics.utah.edu

CONTRACT NUMBER: DK39311 (NIDDK)
HD17463 (NICHD)
M01-RR00064 (NCRR)
+

SOURCE: AMERICAN JOURNAL OF HUMAN GENETICS, **(1997 Sep)** 61 (3) 668-77.
Journal code: 3IM; 0370475. ISSN: 0002-9297.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971105
Last Updated on STN: 19971105
Entered Medline: 19971022

AB Segregation analysis of body-mass index (BMI) supported recessive inheritance of obesity, in pedigrees ascertained through siblings with non-insulin dependent diabetes mellitus (NIDDM). BMI was estimated as 39 kg/m2 for those subjects homozygous at the inferred locus. Two-locus segregation analysis provided weak support for a second recessive locus, with BMI estimated as 32 kg/m2 for homozygotes. NIDDM prevalence was increased among those subjects presumed to be homozygous at either locus. Using both parametric and nonparametric methods, we found no evidence of linkage of obesity to any of nine candidate genes/regions, including the Prader-Willi chromosomal region (PWS), the human homologue of the mouse agouti gene (ASP), and the genes for **leptin** (OB), the **leptin** receptor (OBR/DB), the beta3-adrenergic receptor (ADRB3), lipoprotein lipase (LPL), hepatic lipase (LIPC), glycogen synthase (GYS), and **tumor** necrosis factor alpha (TNFA).

L4 ANSWER 111 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1998:24954 BIOSIS
DOCUMENT NUMBER: PREV199800024954
TITLE: Changes in renal function, **leptin**, cholesterol and TNF-alpha with age in lean and obese hypertensive Zucker rats.

AUTHOR(S): Alavi, F. K. (1); Maddox, D. A.; Leyse, J. W.; Jensen, J. A.; Santella, R. N.; Zawada, E. T., Jr.

CORPORATE SOURCE: (1) Univ. South Dakota Sch. Med., Sioux Falls, SD USA

SOURCE: Journal of the American Society of Nephrology, (**Sept.**, **1997**) Vol. 9, No. PROGRAM AND ABSTR. ISSUE, pp. 610A.
Meeting Info.: 30th Annual Meeting of the American Society of Nephrology San Antonio, Texas, USA November 2-5, 1997 American Society of Nephrology
. ISSN: 1046-6673.

DOCUMENT TYPE: Conference
LANGUAGE: English

DUPLICATE 71

L4 ANSWER 112 OF 159 MEDLINE

ACCESSION NUMBER: 1998140185 MEDLINE
DOCUMENT NUMBER: 98140185 PubMed ID: 9479558

TITLE: Interaction of GLP-I and **leptin** at rat pancreatic B-cells: effects on insulin secretion and signal transduction.

AUTHOR: Fehmann H C; Bode H P; Ebert T; Karl A; Goke B

CORPORATE SOURCE: Department of Medicine, Philipps University of Marburg, Germany.

SOURCE: HORMONE AND METABOLIC RESEARCH, **(1997 Nov)** 29 (11) 572-6.
Journal code: GBD; 0177722. ISSN: 0018-5043.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199804

ENTRY DATE: Entered STN: 19980422
Last Updated on STN: 20000303
Entered Medline: 19980410

AB The incretin effect is reduced in NIDDM, although a corresponding attenuation of incretin hormone secretion does not occur. We characterized the direct interaction of GLP-I, an important incretin hormone, and **leptin** on insulin secretion and signal transduction in B-cells. **Leptin** inhibited GLP-I stimulated insulin release from the isolated perfused rat pancreas. Both phases of the biphasic insulin secretory response were inhibited. GLP-I receptor binding and GLP-I induced cAMP generation remained unchanged. **Leptin** reduced the GLP-I mediated increase of cytosolic Ca2+ concentration. It had similar effects on calcium elevations induced by forskolin. The effect was more pronounced during the plateau phase than during the initial peak. These effects could help to explain **leptin**'s inhibitory effects on insulin secretion. The inhibition of GLP-I's insulinotropic effects by **leptin** may be an interesting aspect in the pathophysiology of NIDDM. The existence of an "adipo-insular axis" is suggested, in which **leptin** represents a negative feed-back signal from the adipose tissue to the endocrine pancreas.

L4 ANSWER 113 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1997:148698 BIOSIS

DOCUMENT NUMBER: PREV199799447901

TITLE: Cachexia in chronic heart failure: **Leptin** mediated anorexia or cytokine and hormone action.

AUTHOR(S): Anker, S. D. (1); Egerer, K. R.; Teixeira, M. M. (1); Hellewell, P. G. (1); Ponikowski, P. (1); Poole-Wilson, P. A. (1); Kox, W. J.; Coats, A. J. S. (1)

CORPORATE SOURCE: (1) NHLI, London UK

SOURCE: Journal of the American College of Cardiology, (1997) Vol. 29, No. 2 SUPPL. A, pp. 501A-502A.
Meeting Info.: 46th Annual Scientific Session of the American College of Cardiology Anaheim, California, USA March 16-19, 1997
ISSN: 0735-1097.

DOCUMENT TYPE: Conference; Abstract; Conference

LANGUAGE: English

L4 ANSWER 114 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1997:186215 BIOSIS

DOCUMENT NUMBER: PREV199799485418

TITLE: Endotoxin induced transcriptional regulation of

leptin and beta-3 adrenergic receptor (b3AR) in mouse adipose tissue.

AUTHOR(S): Berkowitz, Dan; Brown, Dan; An, Ying; Breslow, Michael
CORPORATE SOURCE: Dep. Anesthesiol. Critical Care Med., Johns Hopkins Univ. Sch. Med., Baltimore, MD USA
SOURCE: FASEB Journal, (1997) Vol. 11, No. 3, pp. A437. Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology 97 New Orleans, Louisiana, USA April 6-9, 1997
ISSN: 0892-6638.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L4 ANSWER 115 OF 159 MEDLINE DUPLICATE 72
ACCESSION NUMBER: 1998049840 MEDLINE
DOCUMENT NUMBER: 98049840 PubMed ID: 9388486
TITLE: Transforming growth factor-beta enhances and pro-inflammatory cytokines inhibit ob gene expression in 3T3-L1 adipocytes.
AUTHOR: Granowitz E V
CORPORATE SOURCE: Department of Medicine, Baystate Medical Center, Springfield, Massachusetts, USA..
granowitz@bmcsouth.bhs.org
CONTRACT NUMBER: AI-01288 (NIAID)
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1997 Nov 17)** 240 (2) 382-5.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 20000303
Entered Medline: 19971223

AB **Leptin** is a protein which is encoded by the obese (ob) gene. It is synthesized by adipocytes and binds to receptors in the hypothalamus, thereby suppressing appetite and increasing the metabolic rate. When mouse 3T3-L1 cells are induced to differentiate into adipocytes, they begin to constitutively express low levels of ob mRNA. Using reverse transcription and a semi-quantitative polymerase chain reaction, the experiments described herein demonstrate that the anti-inflammatory cytokine transforming growth factor-beta increases steady state ob mRNA. Conversely, treatment of 3T3-L1 adipocytes with the pro-inflammatory cytokines interleukin-1 beta, interleukin-6, interleukin-11, and **tumor** necrosis factor-alpha results in a decrease in ob transcripts. When considered in the context of animal studies showing that interleukin-1 and **tumor** necrosis factor-alpha induce **leptin** and ob mRNA, these results suggest that pro-inflammatory cytokines induce ob gene transcription in vivo via secondary mediators such as transforming growth factor-beta.

L4 ANSWER 116 OF 159 CANCERLIT
ACCESSION NUMBER: 97622217 CANCERLIT
DOCUMENT NUMBER: 97622217
TITLE: IL-1alpha increases serum **leptin** concentrations

in man (Meeting abstract).
AUTHOR: Janik J E; Curti B D; Gause B L; Kopp W C
CORPORATE SOURCE: NCI-FCRDC, Div. of Clinical Sciences, Frederick, MD.
SOURCE: Proc Annu Meet Am Soc Clin Oncol, **(1997)**. Vol. 16, pp. A371.
ISSN: 0732-183X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199711

AB **Leptin**, the protein product of the ob gene, regulates appetite and body weight. Animals with mutations in the ob gene are obese and lose weight with administration of recombinant **leptin**. Normal animals also lose weight in response to **leptin** administration. **Leptin** can be measured in human serum and its concentration correlates with the percentage of body fat and body mass index. Endotoxin and cytokines induced by endotoxin, IL-1 and TNF, increase expression of **leptin** in hamsters. We hypothesized that serum **leptin** levels might be elevated by cytokine treatment and produce weight loss by causing a reduction in appetite or an increase in metabolism. Serum **leptin** concentrations were measured in patients with **cancer** before and after administration of recombinant human IL-1alpha. Fourteen patients received IL-1alpha at one of three dose levels, 0.03, 0.1 or 0.3 ug/kg/day, for five days. Serum **leptin** concentrations increased in all but one patient within 24 hours after the first dose. The increase in **leptin** was directly correlated with IL-1alpha dose (p=0.0030). Despite continued administration of IL-1alpha, by the final day of treatment serum **leptin** concentrations had returned to pretreatment levels. Anorexia induced by IL-1alpha may be due to this early elevation in serum **leptin** concentration, but continued exposure to IL-1alpha produced tachyphylaxis in the **leptin** response. (C) American Society of Clinical Oncology 1997

L4 ANSWER 117 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:185779 BIOSIS
DOCUMENT NUMBER: PREV199799484982
TITLE: The obesity research: From chambers to atwater to the ob gene.
AUTHOR(S): Stern, Judith S.
CORPORATE SOURCE: Nutr. Dep., Div. Clin. Nutr., Univ. Calif., Davis, CA 95616
USA
SOURCE: FASEB Journal, (1997) Vol. 11, No. 3, pp. A361.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology 97 New Orleans, Louisiana, USA April 6-9, 1997
ISSN: 0892-6638.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L4 ANSWER 118 OF 159 MEDLINE DUPLICATE 73
ACCESSION NUMBER: 97277271 MEDLINE
DOCUMENT NUMBER: 97277271 PubMed ID: 9115396
TITLE: Targeting of **leptin** to the regulated secretory pathway in pituitary AtT-20 cells.
AUTHOR: Chavez R A; Moore H P
CORPORATE SOURCE: 571 Life Sciences Addition, Department of Molecular and Cell Biology, University of California, Berkeley,

California 94720-3200, USA.
CONTRACT NUMBER: GM 35239 (NIGMS)
SOURCE: CURRENT BIOLOGY, **(1997 May 1)** 7 (5) 349-52.
Journal code: B44; 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970709
Last Updated on STN: 20000303
Entered Medline: 19970620

AB **Leptin**, a key regulator of fat homeostasis, is the product of the obese gene [1-3], and is secreted from adipocytes and binds to receptor sites in the choroid plexus [4-5]. Several studies have implicated serum insulin levels in the upregulation of **leptin** gene expression [6-8]. It is currently not known whether **leptin** levels are also subject to regulation at the level of secretion. **Leptin** is normally produced in adipocytes, the secretory pathways of which are not well characterized. Here, we used pituitary AtT-20 cells, which serve as a model system for both regulated and constitutive secretory pathways, to examine the intracellular targeting and secretion of **leptin**. Confocal immunofluorescence analysis of AtT-20 cells expressing an epitope-tagged human **leptin** (FLAG-**leptin**) demonstrated that FLAG-**leptin** colocalized with endogenous adrenocorticotrophic hormone (ACTH) at the tips of processes extended from these cells, where regulated secretory granules accumulate. FLAG-**leptin** secretion was increased in the presence of 8-Br-cAMP, which stimulates the secretion of ACTH. For FLAG-**leptin**, the calculated sorting index, a quantitative measure of the efficiency of protein sorting to the regulated pathway, was similar to those of other regulated secretory proteins. These results demonstrate that FLAG-**leptin** behaves like a regulated protein in cells with a biosynthetic regulated secretory pathway.

L4 ANSWER 119 OF 159 MEDLINE
ACCESSION NUMBER: 97277540 MEDLINE
DOCUMENT NUMBER: 97277540 PubMed ID: 9130924
TITLE: Pediatric obesity. An overview of etiology and treatment.
AUTHOR: Schonfeld-Warden N; Warden C H
CORPORATE SOURCE: Department of Pediatrics, University of California, Davis, Sacramento, USA.
SOURCE: PEDIATRIC CLINICS OF NORTH AMERICA, **(1997 Apr)** 44 (2) 339-61. Ref: 157
Journal code: OUM; 0401126. ISSN: 0031-3955.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970523
Last Updated on STN: 19970523
Entered Medline: 19970515

AB Pediatric obesity is a chronic and growing problem for which new ideas

about the biologic basis of obesity offer hope for effective solutions. Prevalence of pediatric and adult obesity is increasing despite a bewildering array of treatment programs and severe psychosocial and economic costs. The definition of obesity as an increase in fat mass, not just an increase in body weight, has profound influence on the understanding and treatment of obesity. In principle, body weight is determined by a balance between energy expenditure and energy intake, but this observation does not by itself explain obesity. There is surprisingly little evidence that the obese overeat and only some evidence that the obese are more sedentary. Understanding of the biologic basis of obesity has grown rapidly in the last few years, especially with the identification of a novel endocrine pathway involving the adipose tissue secreted hormone **leptin** and the **leptin** receptor that is expressed in the hypothalamus. Plasma **leptin** levels are strongly correlated with body fat mass and are regulated by feeding and fasting, insulin, glucocorticoids, and other factors, consistent with the hypothesis that **leptin** is involved in body weight regulation and may even be a satiety factor (Fig. 2, Table 1). **Leptin** injections have been shown to reduce body weight of primates, although human clinical trials will not be reported until summer 1997. So many peptides influencing feeding have been described that one or more may have therapeutic potential (Fig. 2, Table 1). Although the complexity of pathways regulating body weight homeostasis slowed the pace of understanding underlying mechanisms, these complexities now offer many possibilities for novel therapeutic interventions (Fig. 2). Obesity is a major risk factor for insulin resistance and diabetes, hypertension, **cancer**, gallbladder disease, and atherosclerosis. In particular, adults who were obese as children have increased mortality independent of adult weight. Thus, prevention programs for children and adolescents will have long-term benefits. Treatment programs focus on modification of energy intake and expenditure through decreased calorie intake and exercise programs. Behavior-modification programs have been developed to increase effectiveness of these intake and exercise programs. These programs can produce short-term weight loss. Long-term losses are more modest but achieved more successfully in children than in adults. Several drug therapies for obesity treatment recently have been approved for adults that produce sustained 5% to 10% weight losses but experience with their use in children is limited. Identification of the biochemical pathways causing obesity by genetic approaches could provide the theoretic foundation for novel, safe, and effective obesity treatments. The cloning of **leptin** in 1994 has already led to testing the efficacy of **leptin** in clinical trials that are now underway. Although novel treatments of obesity are being developed as a result of the new biology of obesity, prevention of obesity remains an important goal.

L4 ANSWER 120 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1998:16971 BIOSIS
DOCUMENT NUMBER: PREV199800016971
TITLE: Plasma **leptin** and cachexia in chronic heart failure.
AUTHOR(S): Murdoch, David R.; Rooney, Esther; Dargie, Henry J.; Shapiro, David; Morton, James J.; McMurray, John J. V.
CORPORATE SOURCE: Univ. Glasgow, Glasgow UK
SOURCE: Circulation, (**10/21/97, 1997**) Vol. 96, No. 8 SUPPL., pp. I322.

Meeting Info.: 70th Scientific Sessions of the American Heart Association Orlando, Florida, USA November 9-12, 1997

ISSN: 0009-7322.

DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 121 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:371479 BIOSIS
DOCUMENT NUMBER: PREV199799670682
TITLE: A TNF-alpha gene polymorphism is related with insulin resistance, percent body fat and increased **leptin** .

AUTHOR(S): Gutierrez, C.; Ricart, W.; Casamitjana, R.; Biarnes, J.; Fernandez-Castaner, M.; Vendrell, J.; Richart, C.; Soler, J.; Fernandez-Real, J. M.

CORPORATE SOURCE: Dep. Endocrinol., Hosp. Girona, Hosp. Clinic, Barcelona Spain

SOURCE: Diabetologia, (1997) Vol. 40, No. SUPPL. 1, pp. A305. Meeting Info.: 16th International Diabetes Federation Congress Helsinki, Finland July 20-25, 1997
ISSN: 0012-186X.

DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L4 ANSWER 122 OF 159 MEDLINE DUPLICATE 74
ACCESSION NUMBER: 97478982 MEDLINE
DOCUMENT NUMBER: 97478982 PubMed ID: 9337643
TITLE: Plasma concentration of total **leptin** and human lung-**cancer**-associated cachexia.

AUTHOR: Simons J P; Schols A M; Campfield L A; Wouters E F; Saris W H

CORPORATE SOURCE: Department of Pulmonology, University Hospital, Maastricht, The Netherlands.

SOURCE: CLINICAL SCIENCE, **(1997 Sep)** 93 (3) 273-7.
Journal code: DIZ; 7905731. ISSN: 0143-5221.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 20000303
Entered Medline: 19971113

AB 1. Adipocyte-derived **leptin** is postulated to represent the afferent hormonal signal to the hypothalamus in a feedback mechanism that regulates fat mass. In this proposed feedback mechanism, increased fat mass leads to an elevated plasma **leptin** level that eventually induces a decrease in appetite and an increase in energy expenditure, and vice versa. 2. As anorexia and hypermetabolism play a role in the development of **cancer** cachexia, we investigated the hypothesis that underlying abnormalities in the **leptin** feedback mechanism (in particular relatively high plasma **leptin** levels or, on the other hand, a hypothalamic insensitivity to a fall in **leptin** levels) might be involved. For this purpose, total plasma **leptin** , body composition (fat mass and fat-free mass), appetite and resting

energy expenditure were assessed in 21 male lung-**cancer** patients. 3. Total **leptin** was detectable in six patients and non-detectable in 15. In comparison with the latter, the patients with detectable **leptin** were characterized by a trend towards less weight loss (3.4% compared with 11.0%, P = 0.07), as being less underweight (body mass index 23.8 kg/m2 compared with 19.4 kg/m2, P = 0.004) and by a higher fat mass (21.4 kg compared with 9.7 kg, P = 0.001).

Significant between-group differences in appetite and resting energy expenditure were lacking. 4. Based on these findings, we conclude that in **cancer** the afferent part of the **leptin** feedback mechanism functions normally and that, in particular, elevated **leptin** levels are not involved in the development of cachexia. Since the absence of plasma **leptin** was not associated with an increased appetite and decreased energy expenditure, disturbances in the hypothalamic part of the feedback mechanism are hypothesized.

L4 ANSWER 123 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:371322 BIOSIS
DOCUMENT NUMBER: PREV199799670525
TITLE: Increased plasma **leptin** concentrations in patients with chronic hyperinsulinemia due to insulinoma.
AUTHOR(S): Sbraccia, P. (1); D'Adamo, M. (1); Mellozzi, M. (1); Paoloni, A.; Maroccia, E.; Buongiorno, A.; Tamburrano, G. (1)
CORPORATE SOURCE: (1) Div. Endocrinol. 1, Univ. "La Sapienza", Rome Italy
SOURCE: Diabetologia, (1997) Vol. 40, No. SUPPL. 1, pp. A265. Meeting Info.: 16th International Diabetes Federation Congress Helsinki, Finland July 20-25, 1997
ISSN: 0012-186X.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L4 ANSWER 124 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:475447 BIOSIS
DOCUMENT NUMBER: PREV199799774650
TITLE: Effects of endotoxin and TNF on **leptin** and beta-3 adrenoceptor expression: Possible role in sepsis-induced wasting.
AUTHOR(S): Berkowitz, D.; Brown, D.; Lee, K.; Emala, C.; An, Y.; Breslow, M. J.
CORPORATE SOURCE: Dep. Anesthesiol./CCM, Johns Hopkins Med. Inst., Baltimore, MD 21287-7294 USA
SOURCE: Anesthesiology (Hagerstown), (1997) Vol. 87, No. 3 SUPPL., pp. A261. Meeting Info.: Annual Meeting of the American Society of Anesthesiologists San Diego, California, USA October 18-22, 1997
ISSN: 0003-3022.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L4 ANSWER 125 OF 159 MEDLINE DUPLICATE 75
ACCESSION NUMBER: 1998105085 MEDLINE
DOCUMENT NUMBER: 98105085 PubMed ID: 9442874
TITLE: Adipocyte differentiation and **leptin** expression.

AUTHOR: Hwang C S; Loftus T M; Mandrup S; Lane M D
CORPORATE SOURCE: Department of Biological Chemistry, Johns Hopkins University Medical School, Baltimore, Maryland 21205, USA.
SOURCE: ANNUAL REVIEW OF CELL AND DEVELOPMENTAL BIOLOGY, **(1997)** 13 231-59. Ref: 171
Journal code: CIH; 9600627. ISSN: 1081-0706.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980226
Last Updated on STN: 20000303
Entered Medline: 19980213

AB Adipose tissue has long been known to house the largest energy reserves in the animal body. Recent research indicates that in addition to this role, the adipocyte functions as a global regulator of energy metabolism. Adipose tissue is exquisitely sensitive to a variety of endocrine and paracrine signals, e.g. insulin, glucagon, glucocorticoids, and **tumor** necrosis factor (TNF), that combine to control both the secretion of other regulatory factors and the recruitment and differentiation of new adipocytes. The process of adipocyte differentiation is controlled by a cascade of transcription factors, most notably those of the C/EBP and PPAR families, which combine to regulate each other and to control the expression of adipocyte-specific genes. One such gene, i.e. the obese gene, was recently identified and found to encode a hormone, referred to as **leptin**, that plays a major role in the regulation of energy intake and expenditure. The hormonal and transcriptional control of adipocyte differentiation is discussed, as is the role of **leptin** and other factors secreted by the adipocyte that participate in the regulation of adipose homeostasis.

L4 ANSWER 126 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:61524 BIOSIS
DOCUMENT NUMBER: PREV199800061524
TITLE: Expression of the **leptin** receptor in primary human leukemic blast cells.
AUTHOR(S): Hino, M.; Nakao, T.; Yamane, T.; Tatsumi, N.
CORPORATE SOURCE: Dep. Clinical Hematology, Osaka City Univ. Med. Sch., Osaka Japan
SOURCE: Blood, (**Nov. 15, 1997**) Vol. 90, No. 10 SUPPL. 1 PART 2, pp. 214B-215B.
Meeting Info.: Thirty-ninth Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997 The American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 127 OF 159 MEDLINE
ACCESSION NUMBER: 1999349410 MEDLINE
DOCUMENT NUMBER: 99349410 PubMed ID: 10420925
TITLE: [Nutrition, energy balance, and obesity].

Nutricion, balance energetico y obesidad.
AUTHOR: Fruhbeck G; Sopena M; Martinez J A; Salvador J
CORPORATE SOURCE: Departamento de Fisiologia y Nutricion, Facultad de Medicina, Universidad de Navarra.
SOURCE: REVISTA DE MEDICINA DE LA UNIVERSIDAD DE NAVARRA, **(1997 Jul-Sep)** 41 (3) 185-92. Ref: 78
Journal code: SSG; 0123071. ISSN: 0556-6177.
PUB. COUNTRY: Spain
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Spanish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101
Last Updated on STN: 20000303
Entered Medline: 19991021

AB Energy supply from foods and drinks depends upon carbohydrate, protein, lipid and alcohol content. Cells obtain the energy through a complex and integrated system of physico-chemical processes. The energy value of foods is applied for ATP formation, but also for nutrient utilization and turnover. Net energy from foods is expended for basal metabolism, thermic effect of food and physical activity. Total energy expenditure for human beings is displayed in different lists developed by national and international organisms and institutions. Energy balance and body weight are narrowly interrelated as well as body composition, which depends also of age, sex, exercise and neuroendocrine status. Obesity, is known as an excessive deposition of fat for height, and it is associated with **cancer**, dislipemias, endocrine abnormalities, diabetes, etc. Recent advances suggest that genetic and neuroendocrine factors are more involved in obesity rather than gluttony or sloth as previously reported.

L4 ANSWER 128 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:61381 BIOSIS
DOCUMENT NUMBER: PREV199800061381
TITLE: Dissimilar regulation of **leptin** expression by IL-1 and TNF in humans.
AUTHOR(S): Janik, J. (1); Kopp, W.; Eliot, H.; Alvord, W. G.; Curti, B.; Gause, B.; Elwood, P.; Alexander, H. R.
CORPORATE SOURCE: (1) Med. Branch, Natl. Cancer Inst., Bethesda, MD USA
SOURCE: Blood, (**Nov. 15, 1997**) Vol. 90, No. 10 SUPPL. 1 PART 2, pp. 185B.
Meeting Info.: Thirty-ninth Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997 The American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 129 OF 159 MEDLINE DUPLICATE 76
ACCESSION NUMBER: 97393031 MEDLINE
DOCUMENT NUMBER: 97393031 PubMed ID: 9249548
TITLE: LPS-induced anorexia in **leptin**-deficient (ob/ob) and **leptin** receptor-deficient (db/db) mice.
AUTHOR: Faggioni R; Fuller J; Moser A; Feingold K R; Grunfeld C
CORPORATE SOURCE: Department of Medicine, University of California, USA.
CONTRACT NUMBER: DK-40990 (NIDDK)

DK-49448 (NIDDK)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, **(1997 Jul)** 273 (1 Pt 2) R181-6.
Journal code: 3U8; 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970916
Last Updated on STN: 20000303
Entered Medline: 19970903

AB Administration of endotoxin (lipopolysaccharide, LPS) induces profound anorexia. Injection of **leptin** decreases food intake in mice. Recently, we reported that LPS and cytokines increase **leptin** levels in hamsters. To further investigate the role of **leptin** in the LPS-induced anorexia, we administered LPS to **leptin** receptor-deficient (db/db) and **leptin**-deficient (ob/ob) mice. We found that LPS caused anorexia in both db/db and ob/ob mice. As might be predicted if **leptin** had a role in anorexia, the db/db mice were somewhat resistant to LPS-induced anorexia. However the ob/ob mice were more sensitive to LPS-induced anorexia. No differences between db/db and ob/ob mice and their respective littermate were observed in circulating **tumor** necrosis factor levels after LPS. These data suggest that **leptin** per se is not essential for LPS-induced anorexia.

L4 ANSWER 130 OF 159 MEDLINE DUPLICATE 77
ACCESSION NUMBER: 1998219401 MEDLINE
DOCUMENT NUMBER: 98219401 PubMed ID: 9558706
TITLE: [Obesity genes].
Geny otylosci.
AUTHOR: Swierczynski J; Kochan Z; Karbowska J
CORPORATE SOURCE: Katedra i Zaklad Biochemii A.M. Debinki I, Gdansk.
SOURCE: POSTEPY BIOCHEMII, **(1997)** 43 (3) 174-82. Ref: 66
Journal code: PE4; 0023525. ISSN: 0032-5422.
PUB. COUNTRY: Poland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Polish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980611
Last Updated on STN: 20000303
Entered Medline: 19980602

L4 ANSWER 131 OF 159 MEDLINE DUPLICATE 78
ACCESSION NUMBER: 97149445 MEDLINE
DOCUMENT NUMBER: 97149445 PubMed ID: 8996253
TITLE: Multiple cytokines and acute inflammation raise mouse **leptin** levels: potential role in inflammatory anorexia.
AUTHOR: Sarraf P; Frederich R C; Turner E M; Ma G; Jaskowiak N T; Rivet D J 3rd; Flier J S; Lowell B B; Fraker D L; Alexander H R
CORPORATE SOURCE: Surgical Metabolism Section, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892,

USA.
CONTRACT NUMBER: K08 HL02564 (NHLBI)
P30 DK46200 (NIDDK)
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, **(1997 Jan 6)** 185 (1) 171-5.
Journal code: I2V; 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970227
Last Updated on STN: 20000303
Entered Medline: 19970207

AB Several inflammatory cytokines, most notably **tumor** necrosis factor (TNF) and IL-1, induce anorexia and loss of lean body mass, common manifestations of acute and chronic inflammatory conditions. In C57BL/6 female mice, the administration of TNF, IL-1, and, to a lesser extent, **leukemia** inhibitory factor (LIF), produced a prompt and dose-dependent increase in serum **leptin** levels and **leptin** mRNA expression in fat. IL-10, IL-4, ciliary neurotrophic factor, and IL-2, cytokines not known to induce anorexia or decrease food intake, had no effect on **leptin** gene expression or serum **leptin** levels. After administration of Escherichia coli lipopolysaccharide (LPS), **leptin** gene expression and **leptin** levels were increased. These findings suggest that **leptin** levels may be one mechanism by which anorexia is induced during acute inflammatory conditions.

L4 ANSWER 132 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:229526 BIOSIS
DOCUMENT NUMBER: PREV199799528729
TITLE: Adipose tissue cytokines in hyperthyroidism and hypothyroidism: A possible role for **leptin** in the pathogenesis of energy disequilibrium.
AUTHOR(S): Pinkney, J. H. (1); Mohamed-Ali, V.; Johnson, A. B. (1); Yudkin, J. S.; Lightman, S. L.
CORPORATE SOURCE: (1) Univ. Bristol, Div. Med., Southmead Hosp., London UK
SOURCE: Journal of Endocrinology, (1997) Vol. 152, No. SUPPL., pp. P163.
Meeting Info.: 16th Joint Meeting of the British Endocrine Societies Harrogate, England, UK April 7-10, 1997
ISSN: 0022-0795.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L4 ANSWER 133 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:223281 BIOSIS
DOCUMENT NUMBER: PREV199799514997
TITLE: 100 percent fat: The Keystone Symposium on the Adipose Cell, Park City, Utah, USA (January 15-21, 1997.
AUTHOR(S): Lazar, Mitchell A.
CORPORATE SOURCE: Div. Endocrinol. Diabetes Metab., Dep. Med., Univ. Pa. Sch. Med., 611 CRB, 415 Curie Blvd., Philadelphia, PA 19104-6149
USA
SOURCE: Trends in Genetics, (1997) Vol. 13, No. 4, pp. 137-140.

ISSN: 0168-9525.
DOCUMENT TYPE: Conference; Report
LANGUAGE: English

L4 ANSWER 134 OF 159 MEDLINE DUPLICATE 79
ACCESSION NUMBER: 97382044 MEDLINE
DOCUMENT NUMBER: 97382044 PubMed ID: 9239232
TITLE: **Leptin** and other secretory products of adipocytes modulate multiple physiological functions.
AUTHOR: Weigle D S
CORPORATE SOURCE: Department of Medicine, University of Washington School of Medicine, Seattle, USA.
SOURCE: ANNALES D ENDOCRINOLOGIE, **(1997)** 58 (2) 132-6.
Ref: 34
Journal code: 540; 0116744. ISSN: 0003-4266.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970916
Last Updated on STN: 20000303
Entered Medline: 19970903

AB The view that the adipocyte acts only as a passive storage site for energy in the form of triglyceride has been rendered obsolete by the discovery that adipocytes secrete a variety of metabolically active molecules. These molecules include free fatty acids, which decrease the rate of glucose oxidation by peripheral tissues; adipsin and other complement factors involved in host defense; **tumor** necrosis factor alpha, which may be an important determinant of insulin sensitivity; and angiotensinogen, which appears to promote terminal differentiation of preadipose to adipose cells. **Leptin**, a 167 amino acid polypeptide encoded by the obese gene, is a recently described adipocyte secretory product that communicates the status of the body's energy reserve to the central nervous system, apparently for the purpose of regulating body composition. Plasma **leptin** levels are exponentially related to total adipose mass. Daily injection of **leptin** into ob/ob mice leads to decreased food consumption and increased energy expenditure, both of which result in loss of adipose mass. **Leptin**-treated animals also have lower circulating insulin and glucose levels than pair fed controls. Finally, **leptin** corrects the infertility of ob/ob mice by restoring gonadotropin secretion to normal. These observations indicate that the adipocyte plays a key role in energy balance, insulin action, host defense, and reproduction, and suggest new approaches for understanding several important human diseases.

L4 ANSWER 135 OF 159 MEDLINE DUPLICATE 80
ACCESSION NUMBER: 97190209 MEDLINE
DOCUMENT NUMBER: 97190209 PubMed ID: 9038364
TITLE: **Leptin** receptor (OB-R) oligomerizes with itself but not with its closely related cytokine signal transducer

gp130.

AUTHOR: Nakashima K; Narazaki M; Taga T
CORPORATE SOURCE: Institute for Molecular and Cellular Biology, Osaka University, Suita, Japan.
SOURCE: FEBS LETTERS, **(1997 Feb 10)** 403 (1) 79-82.
Journal code: EUH; 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970327
Last Updated on STN: 20000303
Entered Medline: 19970320

AB **Leptin** (OB) exerts weight-reducing effects in mice. The structure of the receptor for this factor, OB-R, is considerably similar to those of gp130, the common signal transducing receptor component for the interleukin-6 (IL-6) family of cytokines, and **leukemia** inhibitory factor receptor (LIFR). Since the IL-6 family of cytokines signal through gp130 homodimer or gp130/LIFR heterodimer, we have examined in this study the possible involvement of gp130 and LIFR in **leptin** signaling through OB-R. **Leptin** stimulation induces tyrosine phosphorylation of neither gp130 nor LIFR, while LIF stimulation does both. As examined by using two differently epitope-tagged OB-R molecules, the spontaneous homo-oligomerization of OB-R has been elucidated. Ba/F3 cells, which do not express gp130, are non-responsive to **leptin** and exhibit increased DNA synthesis in response to **leptin** after transfection of OB-R cDNA alone. OB-R appears to transduce the signal via its homo-oligomerization without interaction with gp130 or LIFR.

L4 ANSWER 136 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:66606 BIOSIS
DOCUMENT NUMBER: PREV199800066606
TITLE: A functional receptor in AML: Correlation of expression with blast count and FAB M1.
AUTHOR(S): Konopleva, M. (1); Mikhail, A.; Estrov, Z.; Zhao, S.; Harris, D.; Sanchez-Williams, G.; Kornblau, S.; Jung, J.; Kliche, K. O.; Jiang, S.; Przepiorka, D.; Snodgrass, H. R.; Estey, E.; Andreeff, M.
CORPORATE SOURCE: (1) Univ. Texas M.D. Anderson Cancer Cent., Houston, TX USA
SOURCE: Blood, (**Nov. 15, 1997**) Vol. 90, No. 10 SUPPL. 1 PART 1, pp. 68A-69A.
Meeting Info.: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997
The American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 137 OF 159 MEDLINE DUPLICATE 81
ACCESSION NUMBER: 1998051445 MEDLINE
DOCUMENT NUMBER: 98051445 PubMed ID: 9390006
TITLE: Improvement of glucose homeostasis and hepatic insulin resistance in ob/ob mice given oral molybdate.

AUTHOR: Reul B A; Becker D J; Ongemba L N; Bailey C J; Henquin J C;
Brichard S M

CORPORATE SOURCE: Endocrinology and Metabolism Unit, University of Louvain, Faculty of Medicine, Brussels, Belgium.

SOURCE: JOURNAL OF ENDOCRINOLOGY, **(1997 Oct)** 155 (1) 55-64.
Journal code: I1J; 0375363. ISSN: 0022-0795.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 20000303
Entered Medline: 19971217

AB Molybdate (Mo) exerts insulinomimetic effects in vitro. In this study, we evaluated whether Mo can improve glucose homeostasis in genetically obese, insulin-resistant ob/ob mice. Oral administration of Mo (174 mg/kg molybdenum element) for 7 weeks did not affect body weight, but decreased the hyperglycaemia (approximately 20 mM) of obese mice to the levels of lean (L) (+/+) mice, and reduced the hyperinsulinaemia to one-sixth of pretreatment levels. Tolerance to oral glucose was improved: total glucose area was 30% lower in Mo-treated mice than in untreated ob/ob mice (O), while the total insulin area was halved. Hepatic glucokinase (GK) mRNA level and activity were unchanged in O mice compared with L mice, but the mRNA level and activity of L-type pyruvate kinase (L-PK) were increased in O mice by 3.5- and 1.7-fold respectively. Mo treatment increased GK mRNA levels and activity (by approximately 2.2-fold and 61% compared with O values), and had no, or only a mild, effect on the already increased L-PK variables. mRNA levels and activity of the gluconeogenic enzyme, phosphoenolpyruvate carboxykinase (PEPCK) were augmented in O liver (sixfold and by 57% respectively), and these were reduced by Mo treatment.

Insulin binding to partially purified receptors from liver was reduced in O mice and restored by Mo treatment. Despite this correction, overall receptor tyrosine kinase activity was not improved in Mo mice. Moreover, the overexpression (by two- to fourfold) of the cytokine **tumour** necrosis factor alpha (TNF alpha) in white adipose tissue, which may have a determinant role in the insulin resistance of the O mice, was unaffected by Mo. Likewise, overexpression of the ob gene in white adipose tissue was unchanged by Mo. In conclusion, Mo markedly improved glucose homeostasis in the ob/ob mice by an insulin-like action which appeared to be exerted distal to the insulin receptor tyrosine kinase step. The blood glucose-lowering effect of Mo was unrelated to over-expression of the TNF alpha and ob genes in O mice, but resulted at least in part from attenuation of liver insulin resistance by the reversal of pre-translational regulatory defects in these mice.

L4 ANSWER 138 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:373025 BIOSIS
DOCUMENT NUMBER: PREV199799672228
TITLE: Partial GH deficiency and changed **leptin**

sensitivity due to cranial irradiation contribute to overweight after childhood ALL/HNL.

AUTHOR(S): Mayer, E. I. E.; Wiedenmann, S. C.; Dopfer, R. E.; Elmlinger, M. W.; Ranke, M. B.

CORPORATE SOURCE: Univ. Children's Hosp., Tuebingen Germany

SOURCE: Hormone Research (Basel), (1997) Vol. 48, No. SUPPL. 2, pp. 27.
Meeting Info.: 5th Joint Meeting of the European Society for Paediatric Endocrinology and the Lawson Wilkins Society for Pediatric Endocrinology, in Collaboration with the Australian Paediatric Endocrine Group, the Japanese Society for Pediatric Endocrinology and the Latin American Society for Paediatric Endocrinology Stockholm, Sweden June 22-26, 1997
ISSN: 0301-0163.

DOCUMENT TYPE: Conference; Abstract

LANGUAGE: English

L4 ANSWER 139 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1997:82936 BIOSIS

DOCUMENT NUMBER: PREV199799374649

TITLE: Regulation of adipose cell number in man.

AUTHOR(S): Prins, Johannes B.; O'Rahilly, Stephen (1)

CORPORATE SOURCE: (1) Dep. Med. Clin. Biochem., Univ. Cambridge, Level 5, Addenbrooke's Hosp. Hills Rd., Cambridge CB2 2QQ UK

SOURCE: Clinical Science (London), (1997) Vol. 92, No. 1, pp. 3-11.
ISSN: 0143-5221.

DOCUMENT TYPE: General Review

LANGUAGE: English

AB 1. Adipose tissue mass is dependent on both the average volume and the number of its constituent adipocytes. Significant alteration in body mass involves alteration in both adipocyte volume and number. 2. Increases in adipocyte number occur via replication and differentiation of preadipocytes, a process which occurs throughout life. Decreases in adipocyte number occur via preadipocyte and adipocyte apoptosis, and possibly adipocyte dedifferentiation. 3. Overall regulation of adipose mass involves endocrine, paracrine and possibly autocrine systems. Hypothalamic centres appear to control appetite, metabolic rate and activity levels in a coordinated manner. Within the hypothalamus, known weight regulatory molecules include glucagon-like peptide-1, neuropeptide Y and **leptin**. **Leptin** is a major afferent signal from adipose tissue to the hypothalamus, providing information on overall adipose tissue mass. However, the precise means by which the hypothalamus signals to adipose tissue is less well understood. 4. In adipose tissue, known molecular regulators of adipose cell number include insulin, ligands for the peroxisome proliferator activated receptor-7, retinoids, corticosteroids and **tumour** necrosis factor-alpha. The net effect of these and other regulators is to effect a concerted alteration in adipocyte volume and number. This review largely focuses on the control of fat cell acquisition and loss and the influence of these processes on adipose tissue mass and regional distribution.

L4 ANSWER 140 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:182181 BIOSIS
DOCUMENT NUMBER: PREV199800182181
TITLE: 25th Annual Meeting of the Austrian Diabetes Society on the prevention and therapy of Type II Diabetes (Baden bei Wien, Austria; November 13-15, 1997.
AUTHOR(S): Austrian Diabetes Society
SOURCE: Acta Medica Austriaca, (1997) Vol. 24, No. 5, pp. 2-20. ISSN: 0303-8173.
DOCUMENT TYPE: Conference
LANGUAGE: German
AB This meeting contains abstracts of 30 papers and 26 posters, written in German, covering pathophysiology, therapy, insulin, nutrition, **tumor** necrosis factor, **leptin**, hypoglycemia, and metabolism.

L4 ANSWER 141 OF 159 CANCERLIT
ACCESSION NUMBER: 97393031 CANCERLIT
DOCUMENT NUMBER: 97393031
TITLE: LPS-induced anorexia in **leptin**-deficient (ob/ob) and **leptin** receptor-deficient (db/db) mice.
AUTHOR: Faggioni R; Fuller J; Moser A; Feingold K R; Grunfeld C
CORPORATE SOURCE: Department of Medicine, University of California, USA.
CONTRACT NUMBER: DK-40990 (NIDDK)
DK-49448 (NIDDK)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, **(1997)**. 273 (1 Pt. 2):R181-6.
Journal code: 3U8. ISSN: 0002-9513.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDL; L; Priority Journals
LANGUAGE: English
OTHER SOURCE: MEDLINE 97393031
ENTRY MONTH: 199710
AB Administration of endotoxin (lipopolysaccharide, LPS) induces profound anorexia. Injection of **leptin** decreases food intake in mice. Recently, we reported that LPS and cytokines increase **leptin** levels in hamsters. To further investigate the role of **leptin** in the LPS-induced anorexia, we administered LPS to **leptin** receptor-deficient (db/db) and **leptin**-deficient (ob/ob) mice. We found that LPS caused anorexia in both db/db and ob/ob mice. As might be predicted if **leptin** had a role in anorexia, the db/db mice were somewhat resistant to LPS-induced anorexia. However the ob/ob mice were more sensitive to LPS-induced anorexia. No differences between db/db and ob/ob mice and their respective littermate were observed in circulating **tumor** necrosis factor levels after LPS. These data suggest that **leptin** per se is not essential for LPS-induced anorexia.

L4 ANSWER 142 OF 159 LIFESCI COPYRIGHT 2001 CSA
ACCESSION NUMBER: 96:97342 LIFESCI
TITLE: Reflections on STAT3, STAT5, and STAT6 as fat STATs
AUTHOR: Darnell, J.E.,Jr.
CORPORATE SOURCE: Rockefeller Univ., 1230 York Ave., New York, NY 10021, USA
SOURCE: PROC. NATL. ACAD. SCI. USA, (**1996**) vol. 93, no. 13, pp. 6221-6224.
ISSN: 0027-8424.
DOCUMENT TYPE: Journal

FILE SEGMENT: N
LANGUAGE: English
AB The current issue of the Proceedings contains an article entitled "Defective STAT signaling by the **leptin** receptor in diabetic mice" by Ghilardi et al. The reported results suggest how **leptin**, the recently discovered weight control hormone, may signal cells through its cognate receptor by activation of STATs, proteins that serve the dual function of signal transducers and activators of transcription in cells exposed to signaling polypeptides. Mice that produce no **leptin** (obese or ob mutants) weigh up to 60 g instead of the usual 15-20 g for a normal mouse. The human protein is virtually identical to mouse **leptin**, suggesting that the control of body weight in humans may also be regulated by this hormone. The effect of **leptin** on ob mice is to control food intake, so that weight loss ensues. In addition, the mice exhibit increased "mouse-like" exploratory activity. Thus, the description of the first molecule in the weight control pathway opens up the chance to explore in molecular detail the control of a complex behavior. The Ghilardi et al. paper reports confirmatory results showing the presence in cells of widely scattered tissues, including the hypothalamus, the putative control center for feeding behavior, of a "long" and "short" **leptin** receptor. The **leptin** receptor has considerable sequence similarity to the gp130 transmembrane receptor chain that pairs as the signaling molecule with a number of other transmembrane proteins to constitute the receptor for many ligands including interleukin (IL)-6, ciliary neurotrophic factor, **leukemia**-inhibitory factor. The **leptin** receptor appears not to function normally in the mouse mutant termed diabetes (db) because of a base change in an intron that leads to a frequent aberrant splice choice; the resulting mRNA retains a translation stop codon producing a truncated protein lacking approximately 270 amino acids of the cytoplasmic domain of the transmembrane receptor. The omission of these amino acids was hypothesized to prevent intracellular signaling occasioned by **leptin** binding to its cell surface receptor. Based on the homology between the **leptin** receptor and the gp130 transmembrane protein, the pathway through which the **leptin** receptor seemed likely to signal is the recently recognized JAK/STAT pathway. All of the known receptors that contain gp130 have JAK kinases (tyrosine kinases) bound to their intracellular tails. After ligand-mediated receptor assembly, the JAKs become phosphorylated on tyrosine and thereby activated as tyrosine kinases. The intracellular tail of one or more receptor chains is then phosphorylated on one or more tyrosine residues, offering binding sites to the Src homology 2 groups of latent cytoplasmic proteins called STATs. The attached STATs become phosphorylated on tyrosine by the activated Jak kinases. The STATs then dimerize, translocate to the nucleus, and participate in transcriptional regulation by binding to specific DNA sites. In the mutant db receptor both the putative STAT-binding sites and the JAK-binding sites are missing.

DUPLICATE 82

L4 ANSWER 143 OF 159 MEDLINE
ACCESSION NUMBER: 97112359 MEDLINE
DOCUMENT NUMBER: 97112359 PubMed ID: 8954039
TITLE: Serum **leptin** levels in the acquired immunodeficiency syndrome.

AUTHOR: Grunfeld C; Pang M; Shigenaga J K; Jensen P; Lallone R; Friedman J; Feingold K R

CORPORATE SOURCE: Department of Medicine, University of California, San Francisco, USA.

CONTRACT NUMBER: DK-40990 (NIDDK)
DK-41096 (NIDDK)
DK-49448 (NIDDK)

SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, **(1996 Dec)** 81 (12) 4342-6.
Journal code: HRB; 0375362. ISSN: 0021-972X.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 20000303
Entered Medline: 19970106

AB **Leptin**, a hormone that is secreted by adipose tissue in proportion to fat stores, regulates energy balance and appetite. Recently, **tumor** necrosis factor and interleukin-1, cytokines that regulate the host response to infection, have been shown to acutely increase **leptin** levels, raising the possibility that **leptin** could mediate the anorexia of some infections. We measured **leptin** levels in patients with the acquired immunodeficiency syndrome and found that **leptin** levels were not increased relative to body fat in patients who were anorectic, were losing weight, or had a history of weight loss. Furthermore, **leptin** levels were not increased during secondary infection, suggesting that elevations in **leptin** do not play a key role in the anorexia of infections associated with acquired immunodeficiency syndrome.

L4 ANSWER 144 OF 159 LIFESCI COPYRIGHT 2001 CSA

ACCESSION NUMBER: 97:115956 LIFESCI

TITLE: Serum **leptin** levels in the acquired immunodeficiency syndrome

AUTHOR: Grunfeld, C.; Pang, M.; Shigenaga, J.K.; Jensen, P.; Lallone, R.; Friedman, J.; Feingold, K.R.

CORPORATE SOURCE: Metabolism Sect. (111F), Dep. Veterans Affairs Med. Cent., 4150 Clement St., San Francisco, CA 94121, USA

SOURCE: J. CLIN. ENDOCRINOL. METAB., (**19960000**) vol. 8, pp. 4342-4346.
ISSN: 0021-972X.

DOCUMENT TYPE: Journal
FILE SEGMENT: V
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Leptin**, a hormone that is secreted by adipose tissue in proportion to fat stores, regulates energy balance and appetite. Recently, **tumor** necrosis factor and interleukin-1, cytokines that regulate the host response to infection, have been shown to acutely increase **leptin** levels, raising the possibility that **leptin** could mediate the anorexia of some infections. We measured **leptin** levels in patients with the acquired immunodeficiency syndrome and found that **leptin** levels were not increased relative to body fat in patients who were anorectic, were losing weight, or had a history of

weight loss. Furthermore, **leptin** levels were not increased during secondary infection, suggesting that elevations in **leptin** do not play a key role in the anorexia of infections associated with acquired immunodeficiency syndrome.

L4 ANSWER 145 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:318192 BIOSIS
DOCUMENT NUMBER: PREV199699040548
TITLE: Endotoxin and cytokines induce expression of **leptin**, the ob gene product, in hamsters: A role for **leptin** in the anorexia of infection.
AUTHOR(S): Grunfeld, Carl (1); Zhao, Connie; Fuller, John; Pollock, Allan; Moser, Arthur; Friedman, Jeffrey; Feingold, Kenneth R.
CORPORATE SOURCE: (1) Metabolism Section, Dep. Veterans Affairs Med. Cent., 3150 Clement Street, San Francisco, CA 94121 USA
SOURCE: Journal of Clinical Investigation, (1996) Vol. 97, No. 9, pp. 2152-2157.
ISSN: 0021-9738.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The expression of **leptin**, the ob gene product, is increased in adipose tissue in response to feeding and energy repletion, while **leptin** expression decreases during fasting. Infusion of **leptin** decreases food intake. Because adipose tissue gene expression is regulated by cytokines induced during infection and because infection is associated with anorexia, we tested whether induction of **leptin** might occur during the host response to infection. Administration of endotoxin (LPS), a model for gram negative infections, induces profound anorexia and weight loss in hamsters. In fasted animals, LPS increased the expression of **leptin** mRNA in adipose tissue to levels similar to fed control animals. There is a strong inverse correlation between mRNA levels of **leptin** and subsequent food intake. TNF and IL-1, mediators of the host response to LPS, also induced anorexia and increased levels of **leptin** mRNA in adipose tissue. As assessed by immunoprecipitation and Western blotting, circulating **leptin** protein is regulated by LPS and cytokines in parallel to regulation of adipose tissue **leptin** mRNA. Induction of **leptin** during the host response to infection may contribute to the anorexia of infection.

DUPLICATE 83
L4 ANSWER 146 OF 159 MEDLINE
ACCESSION NUMBER: 97053604 MEDLINE
DOCUMENT NUMBER: 97053604 PubMed ID: 8895466
TITLE: Modulation of insulin activities by **leptin**.
COMMENT: Comment in: Science. 1996 Nov 15;274(5290):1151-2
AUTHOR: Cohen B; Novick D; Rubinstein M
CORPORATE SOURCE: Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot 76100, Israel..
lvrub@weizmann.weizmann.ac.il
SOURCE: SCIENCE, **(1996 Nov 15)** 274 (5290) 1185-8.
Journal code: UJ7; 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612

ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 20000303
Entered Medline: 19961210

AB **Leptin** mediates its effects on food intake through the hypothalamic form of its receptor OB-R. Variants of OB-R are found in other tissues, but their function is unknown. Here, an OB-R variant was found in human hepatic cells. Exposure of these cells to **leptin**, at concentrations comparable with those present in obese individuals, caused attenuation of several insulin-induced activities, including tyrosine phosphorylation of the insulin receptor substrate-1 (IRS-1), association of the adapter molecule growth factor receptor-bound protein 2 with IRS-1, and down-regulation of gluconeogenesis. In contrast, **leptin** increased the activity of IRS-1-associated phosphatidylinositol 3-kinase. These in vitro studies raise the possibility that **leptin** modulates insulin activities in obese individuals.

L4 ANSWER 147 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:17455 BIOSIS
DOCUMENT NUMBER: PREV199799316658
TITLE: Does **leptin** contribute to diabetes caused by obesity.
AUTHOR(S): Taylor, Simeon I.; Barr, Valarie; Reitman, Marc
CORPORATE SOURCE: Diabetes Branch, Natl. Inst. Diabetes and Digestive and Kidney Diseases, Natl. Inst. Health, Bethesda, MD 20892-1829 USA
SOURCE: Science (Washington D C), (1996) Vol. 274, No. 5290, pp. 1151-1152.
ISSN: 0036-8075.
DOCUMENT TYPE: Journal; Article
LANGUAGE: English

L4 ANSWER 148 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:44544 BIOSIS
DOCUMENT NUMBER: PREV199799343747
TITLE: The endocrinology of obesity.
AUTHOR(S): Smith, Steven R.
CORPORATE SOURCE: Pennington Biomed. Res. Cent., 6400 Perkins Road, Baton Rouge, LA 70808 USA
SOURCE: Endocrinology and Metabolism Clinics of North America, (1996) Vol. 25, No. 4, pp. 921-942.
ISSN: 0889-8529.
DOCUMENT TYPE: General Review
LANGUAGE: English

L4 ANSWER 149 OF 159 MEDLINE DUPLICATE 84
ACCESSION NUMBER: 97096342 MEDLINE
DOCUMENT NUMBER: 97096342 PubMed ID: 8941366
TITLE: **Leptin** induces tyrosine phosphorylation of cellular proteins including STAT-1 in human renal **adenocarcinoma** cells, ACHN.
AUTHOR: Takahashi Y; Okimura Y; Mizuno I; Takahashi T; Kaji H; Uchiyama T; Abe H; Chihara K
CORPORATE SOURCE: Department of Medicine, Kobe University School of Medicine, Japan.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS,

(1996 Nov 21) 228 (3) 859-64.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 20000303
Entered Medline: 19970106

AB Several lines of evidence from in vivo animal experiments and human studies suggest that **leptin**, a peptide secreted from adipose tissue, plays a role in regulating food intake and energy expenditure. However, the signal transduction mechanism of **leptin** in its target cells remains unknown thus far since **leptin**-responsive cell lines have not been available yet. We found that **leptin** caused the tyrosine phosphorylation of several proteins in human renal cell **carcinoma** cells, ACHN cells, in which STAT-1, but neither STAT-3 nor STAT-5, was involved. An ACHN cell line would serve as a useful tool for analyzing the signal transduction mechanism of **leptin**.

L4 ANSWER 150 OF 159 MEDLINE DUPLICATE 85
ACCESSION NUMBER: 97165861 MEDLINE
DOCUMENT NUMBER: 97165861 PubMed ID: 9013754
TITLE: Circulating TNF-alpha and **leptin** levels in offspring of NIDDM patients do not correlate to individual insulin sensitivity.

AUTHOR: Kellerer M; Rett K; Renn W; Groop L; Haring H U
CORPORATE SOURCE: Medizinische Klinik und Poliklinik, Abt. Innere IV, Universitat Tubingen, Germany.

SOURCE: HORMONE AND METABOLIC RESEARCH, **(1996 Dec)** 28 (12) 737-43.
Journal code: GBD; 0177722. ISSN: 0018-5043.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970422
Last Updated on STN: 20000303
Entered Medline: 19970410

AB Obesity plays a central role in the development of skeletal muscle insulin resistance. The molecular mechanism causing skeletal muscle insulin resistance in obese people is still poorly understood. It has been speculated that circulating factors derived from adipose tissue impair insulin signalling in the skeletal muscle cell. TNF-alpha and **leptin**, which are overproduced in fat tissue of obese insulin resistant animal models and in obese humans, might mediate such an inhibitory effect on insulin signalling in skeletal muscle. The aim of the present study was to evaluate whether circulating TNF-alpha and **leptin** correlates to the individual skeletal muscle insulin sensitivity in individuals with different degrees of obesity and insulin resistance. We measured circulating TNF-alpha and **leptin** values in non diabetic offsprings of NIDDM patients. 36 German and 47 Finnish subjects participated in the study. The GDR of each participant was

determined by the euglycemic hyperinsulinemic clamp technique, a range between 1.37 to 14.01 mg/kg LBM x min was observed. Percent of desirable body weight (PDW) covered also a wide range (87.58% to 197.06%). Although linear regression analysis suggested a dependence between TNF-alpha and GDR (Germany group: r = -0.37, p < 0.05, Finnish group: r = -0.32, p < 0.05) and a dependence between TNF and PDW (German group: r = 0.46, p < 0.05, Finnish group: r = 0.38, p < 0.05), in multiple linear regression analysis only the correlation with PDW was significant. **Leptin** levels were measured from 29 German and 36 Finnish subjects and a strong association was found between **leptin** and PDW (German group: r = 0.55, p < 0.05, Finnish group: r = 0.73, p < 0.05). In contrast, **leptin** levels did not correlate with GDR and TNF-alpha. In summary, even though, in a few insulin resistant subjects, higher circulating TNF-alpha or **leptin** levels with the individual insulin sensitivity can be demonstrated, the data suggest that the circulating pool of TNF-alpha and **leptin** in blood is unlikely to be a major contributing factor for obesity induced insulin resistance in the vast majority of individuals at high risk to develop NIDDM.

L4 ANSWER 151 OF 159 MEDLINE DUPLICATE 86
ACCESSION NUMBER: 97165849 MEDLINE
DOCUMENT NUMBER: 97165849 PubMed ID: 9013742
TITLE: Regulation of **leptin** production in cultured mature white adipocytes.
AUTHOR: Hardie L J; Guilhot N; Trayhurn P
CORPORATE SOURCE: Division of Biochemical Sciences, Rowett Research Institute, Bucksburn, Aberdeen, Scotland, United Kingdom.
SOURCE: HORMONE AND METABOLIC RESEARCH, **(1996 Dec)** 28 (12) 685-9.
Journal code: GBD; 0177722. ISSN: 0018-5043.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970422
Last Updated on STN: 20000303
Entered Medline: 19970410

AB A 96-well plate format system is described for the in vitro culture and analysis of **leptin** secretion by mature adipocytes. Cultured adipocytes secreted **leptin** in a linear fashion over a 48 h period and secretion was inhibited by actinomycin D treatment. Dexamethasone and insulin stimulated **leptin** production in vitro, with dexamethasone proving a more potent stimulus throughout. Culture of adipocytes with insulin and dexamethasone together resulted in an additive release of **leptin**, suggesting that stimulation by these factors operates via independent routes. Isoprenaline (1 - 1000 microM) was a potent inhibitor of **leptin** production but propanolol (3 microM) could block this inhibition. Inclusion of growth hormone, insulin-like growth factor 1 or **tumor** necrosis factor alpha did not affect **leptin** secretion by mature adipocytes.

L4 ANSWER 152 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:495537 BIOSIS
DOCUMENT NUMBER: PREV199699217893
TITLE: Cytokine-induced anorexia: 1) cytokine-cytokine interactions: 2. cytokine-NPY interactions: 3. anorexia

induced by activators of the signal transducer GP 130 (used by IL-6 family receptor members) that shares homology with a **leptin** receptor.

AUTHOR(S): Sonti, G.; Ilyin, S. E.; Plata-Salaman, C. R.
CORPORATE SOURCE: Sch. Life Health Sci., Univ. Delaware, Newark, DE 19716-2590 USA
SOURCE: Society for Neuroscience Abstracts, (1996) Vol. 22, No. 1-3, pp. 460.
Meeting Info.: 26th Annual Meeting of the Society for Neuroscience Washington, D.C., USA November 16-21, 1996
ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 153 OF 159 LIFESCI COPYRIGHT 2001 CSA
ACCESSION NUMBER: 96:95431 LIFESCI
TITLE: Calories lost - Another mediator of **cancer** cachexia?
AUTHOR: Nabel, G.J.; Grunfeld, C.
CORPORATE SOURCE: Howard Hughes Med. Inst., Univ. Michigan Med. Cent., 1150 W. Med. Cent. Dr., Ann Arbor, MI 48109-0650, USA
SOURCE: NAT. MED., (**1996**) vol. 2, no. 4, pp. 397-398.
ISSN: 1078-8956.
DOCUMENT TYPE: Journal
FILE SEGMENT: B
LANGUAGE: English

AB Cachexia is among the most visible and devastating consequences of several human diseases. It is a prominent feature of **cancer**, chronic parasitic infections and vital diseases, including acquired immunodeficiency syndrome (AIDS). The cachectic process results in significant morbidity and increased mortality in association with these diseases. The syndrome of cachexia is complex and involves multiple mechanisms, including loss of appetite (anorexia), weight loss, muscle wasting, weakness, hematological abnormalities including anemia, and abnormalities in protein, lipid and carbohydrate metabolism. Superficially, the problem of cachexia appears simple - the degree of caloric intake is not sufficient to match the metabolic expenditure, resulting in a net loss of calories. However, the specific molecular mechanism by which this occurs is less clear. Several candidate molecules, mostly cytokines, have been proposed to mediate this effect and while more attention has focused on **tumor** necrosis factor (TNF), other cytokines implicated include interleukin-6, interleukin-1 (IL-1), and interferon- gamma . More recently, exciting work regarding molecules that may regulate appetite and weight control because of their effects on metabolism and the endocrine system have also been identified. Notably, the **leptin** molecule and its putative receptor appear to play a major role in maintaining normal weight. Mutations in these gene products result in abnormalities in weight control and result in the phenotype observed in the obese (ob) mouse. Expression of **leptin** is increased in response to endotoxin, TNF and IL-1, suggesting a role for **leptin** in the anorexia of infection or **cancer**. A provocative report of yet another potential mediator of **cancer** cachexia has now appeared, based on the observation that a murine **adenocarcinoma**, MAC16 induces significant weight loss in

tumor-bearing mice. Initial studies showed that transplantation into mice of MAC16 **tumor** cells led to a significant and delayed cachexia in the absence of severe anorexia. In addition, a monoclonal antibody was derived from **tumor**-challenged mice that was able to neutralize this effect. Evidence was obtained that this weight loss was mediated through a circulating factor. In a recent report in Nature, Todorov and colleagues have now biochemically identified this cachectic factor as a proteoglycan and have begun its characterization. Purified to homogeneity, this molecule causes substantial acute weight loss when injected intravenously into recipient mice. Even more provocative is the finding that a similar immunoreactive substance can be detected in the urine of patients with cachexia associated with malignancy but is not found in patients with malignancy without weight loss, or in patients with weight loss attributable to other causes. This factor is associated with cachexia in both mouse and humans, and will undoubtedly be the subject of considerable scrutiny. Specifically, it will be important to define its role more broadly in different human malignancies and to define its mechanism of action more precisely.

L4 ANSWER 154 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:351611 BIOSIS
DOCUMENT NUMBER: PREV199699073967
TITLE: LPS, TNF and IL-1 induce expression of **leptin**, the ob gene product, in hamsters: A role for **leptin** in the anorexia of infection.
AUTHOR(S): Grunfeld, C. (1); Zhao, C.; Fuller, J.; Pollack, A.; Moser, A.; Friedman, J.; Feingold, K. R.
CORPORATE SOURCE: (1) Dep. Med., Univ. Calif., San Francisco, CA USA
SOURCE: European Cytokine Network, (1996) Vol. 7, No. 2, pp. 258. Meeting Info.: 6th International Tumor Necrosis Factor Congress Rhodes, Greece May 8-12, 1996
ISSN: 1148-5493.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 155 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:451892 BIOSIS
DOCUMENT NUMBER: PREV199699174248
TITLE: RT-PCR analysis of tissue specific gene expression on microspecimen of subcutaneous depots in obese subjects.
AUTHOR(S): Napolitano, A.; Maffei, P.; Perin, R.; Martini, C.; De Carlo, E.; Scandellari, C.; Sicolo, N.
CORPORATE SOURCE: 1st. Semeiotica Med., Patol. Med. III, Univ. Padua, Padua Italy
SOURCE: Diabetologia, (1996) Vol. 39, No. SUPPL. 1, pp. A170. Meeting Info.: 32nd Annual Meeting of the European Association for the Study of Diabetes Vienna, Austria September 1-5, 1996
ISSN: 0012-186X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 156 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:496145 BIOSIS
DOCUMENT NUMBER: PREV199699218501
TITLE: Secretion of **leptin** and TNF-alpha by the

adipocyte in vitro: Regulation within genetic and dietary-induced obesity.
AUTHOR(S): Houseknecht, K. L.; Flier, S. N.; Frevert, E. U.; Frederich, R. C.; Flier, J. S.; Kahn, B. B.
CORPORATE SOURCE: Beth Israel Hosp., Boston, MA USA
SOURCE: Journal of Animal Science, (1996) Vol. 74, No. SUPPL. 1, pp. 150.
Meeting Info.: 88th Annual Meeting of the American Society of Animal Science Rapid City, South Dakota, USA July 24-26,
1996
ISSN: 0021-8812.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 157 OF 159 MEDLINE
ACCESSION NUMBER: 97075791 MEDLINE
DOCUMENT NUMBER: 97075791 PubMed ID: 8918182
TITLE: Why is the treatment of **cancer** more successful than that of obesity?.
AUTHOR: Berry E M
CORPORATE SOURCE: Department of Human Nutrition and Metabolism, Hebrew University-Hadassah Medical School, Jerusalem, Israel.
SOURCE: PUBLIC HEALTH REVIEWS, **(1996)** 24 (2) 147-63.
Ref: 29
Journal code: Q9E; 0370123. ISSN: 0301-0422.
PUB. COUNTRY: Israel
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 20000303
Entered Medline: 19970102

L4 ANSWER 158 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:500907 BIOSIS
DOCUMENT NUMBER: PREV199699223263
TITLE: TNF-alpha and **leptin** in adjuvant arthritis (AA): Implications for inflammatory cachexia.
AUTHOR(S): Roubenoff, R. (1); Edwards, C. K.; Kehayias, J. J.; Smith, D. E.; Abad, L. W.; Bendele, A.; Bucher, C.; Nicolson, M.; Frazier, J.; Dinarello, C. A.
CORPORATE SOURCE: (1) Human Nutrition Res. Cent., Tufts Univ., Boston, MA 02111 USA
SOURCE: Arthritis & Rheumatism, (1996) Vol. 39, No. 9 SUPPL., pp. S77.
Meeting Info.: 60th National Scientific Meeting of the American College of Rheumatology and the 31st National Scientific Meeting of the Association of Rheumatology Health Professionals Orlando, Florida, USA October 18-22, 1996
ISSN: 0004-3591.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 159 OF 159 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 1997:18885 BIOSIS

DOCUMENT NUMBER: PREV199799318088

TITLE: Obese gene expression is acutely regulated by **tumor** necrosis factor during sublethal endotoxemia in mice.

AUTHOR(S): Ma, Grace; Turner, Ewa; Jaskowiak, Nora; Sarraf, Pasha; Bartlett, David; Fraker, Douglas; Alexander, H. Richard

CORPORATE SOURCE: Surg. Metab. Sect., Surg. Branch, Natl. Cancer Inst., Natl. Inst. Health, Bethesda, MD USA

SOURCE: Surgical Forum, (1996) Vol. 47, No. 0, pp. 17-20. ISSN: 0071-8041.

DOCUMENT TYPE: Article

LANGUAGE: English